

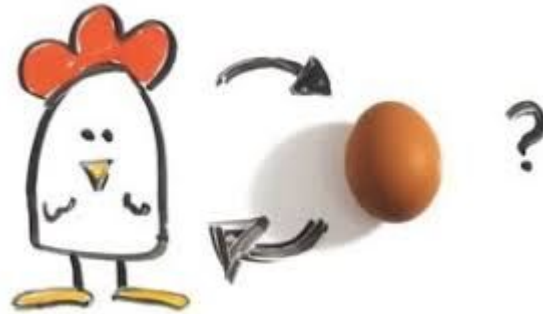
# The Gut Microbiome

March 12, 2020

“My Microbiome is.....

- making me gain weight”
- causing my diabetes”
- causing almost every problem imaginable....”

But which came first –



## **Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain**

C Menni, M A Jackson, T Pallister, C J Steves, T D Spector & A M Valdes

- In the largest study to date, we have profiled the effects of gut microbiome diversity and dietary fibre intake on longitudinal weight gain.
  - We showed that long-term weight gain is only in part determined by an individual's genetic make-up and that **low gut microbiome diversity is associated with a higher weight gain over time.**
- We note two possible interpretations for the data reported.
  - Gut microbiome composition could contribute to weight gain independently of calorie intake, physical activity and other potential confounders (such as, use of proton pump inhibitors or antibiotics).
  - An alternative interpretation is that weight gain may be contributing to lower bacterial diversity.
- Suggest that **gut microbes may be viewed as 'novel' future therapeutic target to treat obesity.**

# Ads for Products to Fix your Microbiome & Your Problems

## See microbiome superfoods



Viome At Home  
Microbiome G...  
**\$129.00**  
Viome  
Free shipping



Plant Based  
Protein Powde...  
**\$129.90**  
Your Superfoods  
★★★★★ (85)



Ultimate Health  
Bundle - Boost...  
**\$289.90**  
Your Superfoods  
★★★★★ (602)



Genuine Health  
Ferme  
**\$34.9:**  
Vitaco  
Spe



MegaPreBiotic

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## See probiotics for diabetes

Ads ⓘ



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1MD



Nature's Way  
Probiotic ...  
**\$9.19**  
Swanson He...



Renew Life  
Ultimate Flor...  
**\$16.98**  
Renew Life



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Acupuncture ...



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Complete ...  
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# What Is the Gut Microbiome?

- The gut microbiome refers to all the microbes in the intestines:
  - Bacteria, viruses, fungi and other microscopic living things are referred to as *microorganisms, or microbes*, for short - Trillions of these microbes exist mainly inside the intestines and on the skin.
- There are **roughly 40 trillion bacterial cells in the body** and only 30 trillion human cells.
  - That means more bacterial cells than human cells
  - These microbes may weigh as much as 2–5 pounds (1–2 kg), which is roughly the weight of the brain.
  - They function as an **extra organ** in the body and play a huge role in health.

# The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes

Ömrüm Aydın, Max Nieuwdorp and Victor Gerdes

- The **gut microbiota** is a collective term for the microbial community in the gut
  - the **gut microbiome** is defined as the **full collection of genes in the gut microbiota**.
- The microbiota act as a microbial organ living symbiotically inside our gut - this *intimate co-evolution* has led to an interlocked **symbiotic relationship**, with diverse capacities including:
  - degradation of otherwise indigestible components of our diet
  - harvesting of energy and nutrients
  - shaping of the host immune system
  - maintaining the integrity of the gut mucosal barrier
  - xenobiotic metabolism
- Thus, gut microbiota complement our biology in ways that are **mutually beneficial**

## The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes continued

- Gut microbes in the healthy human population are of diverse composition and somewhat unique to individuals with a “***personal microbiota***” .
  - Despite the **interpersonal variation**, the gut microbiota maintain a stable relative abundance at operational taxonomic unit levels.
    - **Five phyla dominate** the microbial community: **Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, and Verrucomicrobia.**
- Rapid luminal flow, high acidity, and secretion of bile acids and other compounds cause a *changing microbial density along the gastrointestinal (GI) tract* **with low density in the upper GI tract and it expands towards the rectum.**
  - The **proximal part of the GI tract** is enriched with Lactobacillaceae (belonging to Firmicutes) and proteobacteria (Enterobacteriaceae),
  - The more **distal large intestine** shows higher concentrations of Firmicutes (Lachnospiraceae, Ruminococcaceae) and anaerobes such as Bacteroidetes (Bacteroidaceae, Prevotellaceae, and Rikenellaceae).

## The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes continued

- The **Human Microbiome Project (HMP)** from the USA as well as **LIFELINES**, and the **Flemish Gut flora** cohorts in Europe - creating a **catalogue of the human microbiota**.
- Symbionts and commensals [beneficial] are not the only microorganisms the host encounters. The **host immune system** is continuously challenged by ***distinguishing beneficial microbes from pathogens***.
- Although *still poorly understood*, the gut microbiota and the host immune system have **co-evolved** so profoundly that they can influence our ***immunological well-being***.
  - This is seen in germ-free mice, where the **absence of a microbiota** leads to **defects in the development and function of the immune system**.
  - This **dynamic maturation** of the gut microbiome and host immune system is determining **host-microbe interactions** and influencing the **susceptibility to infection, inflammatory diseases, and autoimmunity**.



## The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes continued

- There are different **factors influencing the development of the microbiome** in the **early years of life**, starting with
  - the mode of birth [vaginal delivery vs c-section]
  - breastfeeding or formula-feeding infants
  - possibly the introduction of solid food
- The intestinal microbiome stabilizes about 3 years after birth, when it resembles the adult microbiome and stays relatively stable over time
- In **adulthood**, the microbiome can be altered by
  - changes in **diet**
  - use of several types of **medication** such as antibiotics, metformin, and even proton pump inhibitors;
    - **Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug.** Wu H, et al Nat Med. 2017 Jul; 23(7):850-858.
- Nonetheless, **only 18.7% of the interpersonal variation** in microbial composition could be explained **by host characteristics** (physiologic and biomedical measures), previous diseases, medication use, smoking, and dietary factors.

Diet is a modulator of the composition and the function of the gut microbiota.

- Microbiota alters rapidly when exposed to changes in diet.
  - Short-term dietary changes such as switching between plant- and meat-based diets or adding more than 30 grams of fiber per day to the diet or following a diet with a different fat/fiber content can change the human gut microbiota in function and composition significantly in 48 hours.
- However, only ***long-term dietary habits are most important*** in actually shaping the composition of the gut microbiota.
  - Short-term dietary interventions failed to change the major features and classification of the microbiota.
  - Another aspect to consider is the **high interpersonal variance in the effect of changed diets on the gut flora**, thus *mirroring the individualized nature of our gut microbiota*.

## The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes continued

- It is thought that **(aromatic) metabolites derived from gut microbiota** processing of dietary compounds are important factors ***influencing host physiology***; conversely, the responses to nutrients are influenced by the gut microbiota.
  - **Choline** and **trimethylamine-N-oxide (TMAO)** are two of those impacting micronutrients. For example:
    - A **choline-deficient diet** in humans **modulates the gut bacteria with altered levels** of Gammaproteobacteria and Erysipelotrichi and this is directly associated with **fatty liver development**.
    - A diet which resulted in **increased levels of TMAO** in plasma **enhanced atherosclerotic plaques**
- Several studies, mostly animal models, demonstrated the microbiota as a major factor in the **development of obesity**.
  - This is illustrated in a study on **genetically obese ob/ob mice, which had a 50% reduction of Bacteroidetes and an increase of Firmicutes in comparison to their lean siblings**.
  - These differences affect the metabolic potential of the gut microbiota, and these ob/ob mice are known to have an **increased capacity in harvesting energy** from ingested food - a trait which appeared to be **transmissible** to germ-free mice through **microbiota transplantation resulting in increase of obesity**.

- These data should be interpreted with **caution**.
  - A meta-analysis from 4 studies confirmed the differences in phylum-level taxonomic composition between lean and obese subjects. However, it ***could not reproduce the association between BMI and taxonomic composition.***
  - ***Composition of the gut microbiota does not always translate into function.***
- In conclusion, in the past decade, animal and human studies have ***identified relevant differences in intestinal microbiota composition in subjects with obesity and T2D.***
- However, **the causality and magnitude of effect on metabolic function remains to be proven.**

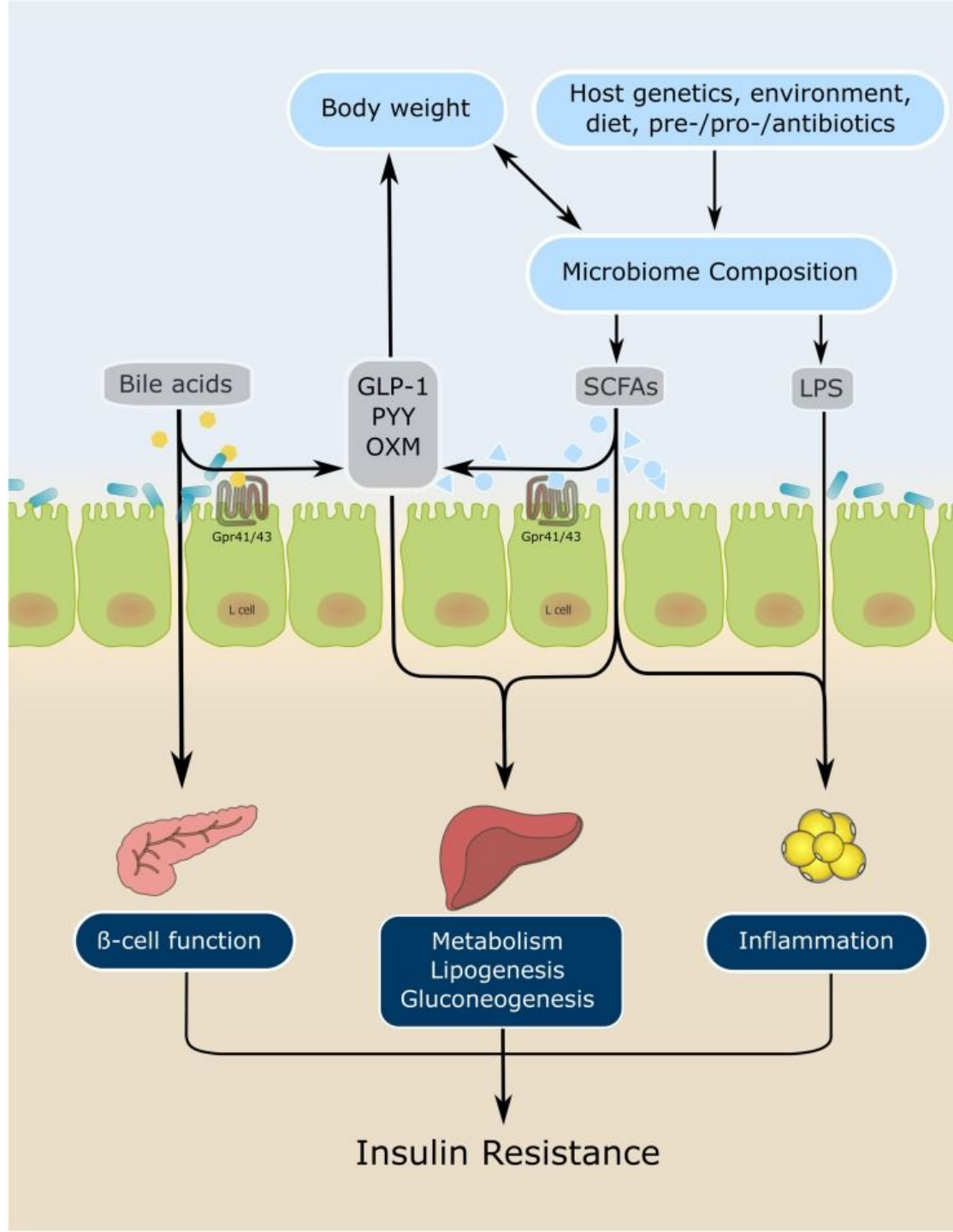
# The Gut Microbiome and Diabetes

Maria Muccioli Ph.D. February 27th, 2019

Reviewing comprehensive lit review from Frontiers in Endocrinology

Certain microorganisms can participate in blood glucose regulation via:

- **Incretin Production:** Incretins are molecules that help increase insulin production. They are usually produced in the gut in response to a meal. Incretin production is more likely to be impaired in people with type 2 diabetes. Because “**some bacteria can directly regulate incretin secretion by the metabolic compounds they produce**”.
- **Short-Chain Fatty Acid (SCFA) Production:** Experts explain that “the host diet provides non-digestible dietary fibers to promote bacterial growth and, in turn, the gut bacteria generate SCFA that can be used as substrates by the host.” Interestingly, these molecules have been shown to be important for blood glucose regulation.
- **Bile Acid Metabolism:** a lot of research is still ongoing and many gaps in the knowledge remain, but “a growing body of evidence suggests that microbiota-bile acids interactions play also a role in the rapid improvement of glycemic control after bariatric surgery... [and] bile acid homeostasis is another piece in the puzzle linking microbiota, and host glycemic control.”
- **Adipose Tissue Regulation:** certain microorganisms can regulate adipose tissue inflammation and function.

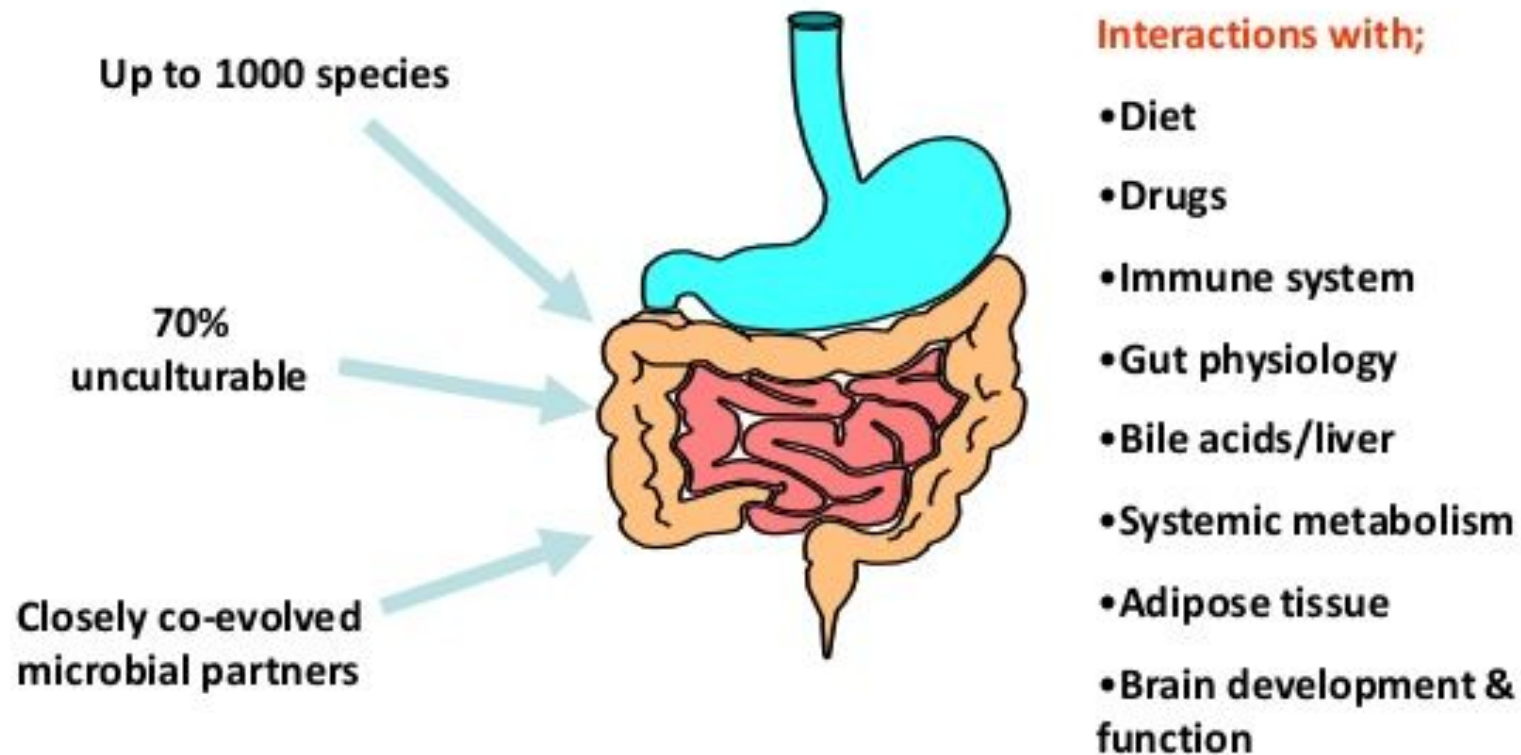


# Summary



- Recent quote: *"There is **still the question** of whether the **specific microbiota** associated with [XXX disorder] is **the cause or the result of the disease**; therefore, more research is needed..."*
- Our gut microbiome contributes **one part of the picture** [no *"magic microbiome pills"* will allow you to eat all you want & lose weight] – works with other factors - **synergy effects/mutuality**
- **What about Probiotics or Fecal Transplant?**
  - Fecal Transplant research ongoing – C. diff
  - ***"The Probiotic Conundrum"*** JAMA March 3, 2000 Vol 323, No 9, page 823
    - Marketed as dietary supplements: structure-function claims without FDA approval – without evidence - over \$64 Billion in revenues worldwide
    - Lack of high-quality (low-risk-of-bias) trials – fewer and fewer human studies
    - "can't hurt, might help" attitude may not hold – safety concerns surfacing

# The human gut microbiome





# Reports on Microbiome

Extra slides

# Study links Mediterranean diet to improved microbiome

- 2/24/2020
- Research published in the journal Gut found following a Mediterranean diet for one year was associated with ***changes in the gut microbiome linked to improved cognitive function, slowed signs of frailty and reduced production of inflammatory markers.***
  - The study, which included more than 600 older adults, found the results were consistent regardless of where people lived, their age or weight.

January 22, 2020

## Is Early-Life Antibiotic Exposure Associated With Obesity in Children?

Meghan B. Azad, PhD<sup>1,2</sup>; Arthur Owora, DrPH<sup>3</sup>

JAMA Netw Open. 2020;3(1):e1919694. doi:10.1001/jamanetworkopen.2019.19694

- Interest in the microbiome and its role in the developmental origins of obesity has increased substantially in the past decade, prompting multiple studies on early-life antibiotic exposures and childhood obesity.
  - There are 2 new reports using prescription records to assess antibiotic exposures in New Zealand: a prospective cohort study of 5128 children by Chelimo et al and a retrospective national study of 284 211 mothers and children by Leong et al.
- Both studies ***found dose-dependent associations between early antibiotic exposure*** (prenatally or during the first 1-2 years of life) and ***body mass index or obesity at age 4 to 5 years***.
- However, when Leong et al ***restricted their analysis to siblings and twins***, they found **no significant association**, suggesting that the association between antibiotics and obesity may be due to ***unmeasured confounding factors that are shared within families***

# Review - Microbiome and type 1 diabetes

Heli et al

<https://doi.org/10.1016/j.ebiom.2019.06.031>

- Even though reports on the **T1D-related changes in the gut microbiota** are accumulating, *proving the causality* has remained challenging.
  - Causality requires that when all possible confounders have been controlled for, ceteris paribus (other things being equal), change in one variable should lead to change in another variable in a repeatable and generalizable way.
    - As long as no randomized, controlled, placebo-controlled intervention studies showing long-term changes in the intestinal microbial colonization and in the immunological maturation that lead repeatedly to comparable changes in the T1D-associated outcomes have been performed in man, **causality between dysbiosis and T1D remains open.**

# Study links altered gut microbiome to PCOS in girls with obesity

- A study that included 58 adolescent girls with obesity found those ***with polycystic ovary syndrome*** had a **different gut microbiome** than those ***without PCOS who had a similar BMI and dietary habits***, researchers reported in The Journal of Clinical Endocrinology & Metabolism.
  - "As in the setting of other infectious or metabolic diseases, we need to test if shifting the microbiome to a more healthy-profile via diet or medication improves PCOS or metabolic syndrome," said researcher Dr. Melanie Cree-Green.

# **Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism**

T. Andrew Clayton, David Baker, John C. Lindon, Jeremy R. Everett, and Jeremy K. Nicholson,  
Research and Development, Ramsgate Road, Sandwich, KentCT13 9NJ, United Kingdom

- We propose that assessing the effects of microbiome activity should be an integral part of pharmaceutical development and of personalized health care.
- Furthermore, we envisage that gut bacterial populations might be deliberately manipulated to improve drug efficacy and to reduce adverse drug reactions

- **Sugar-sweetened Beverage and High Fat Diet Consumption Harmfully Alters Gut Microbiota and Promotes Gut Inflammation (P20-041-19)**
- Woo-Jeong Shon, Min Ho Jung, Eun Young Choi, Dong-Mi Shin
- *Current Developments in Nutrition*, Volume 3, Issue Supplement\_1, June 2019, nzz040.P20-041-19, <https://doi.org/10.1093/cdn/nzz040.P20-041-19>
- **Published:**
- 13 June 2019