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New ways to understand how foods affect me and my health!

Edited by
Lorraine Brennan, Kathryn Burton-Pimentel, Marjukka Kolehmainen, Fiona Malcomson and John Mathers

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Human Health

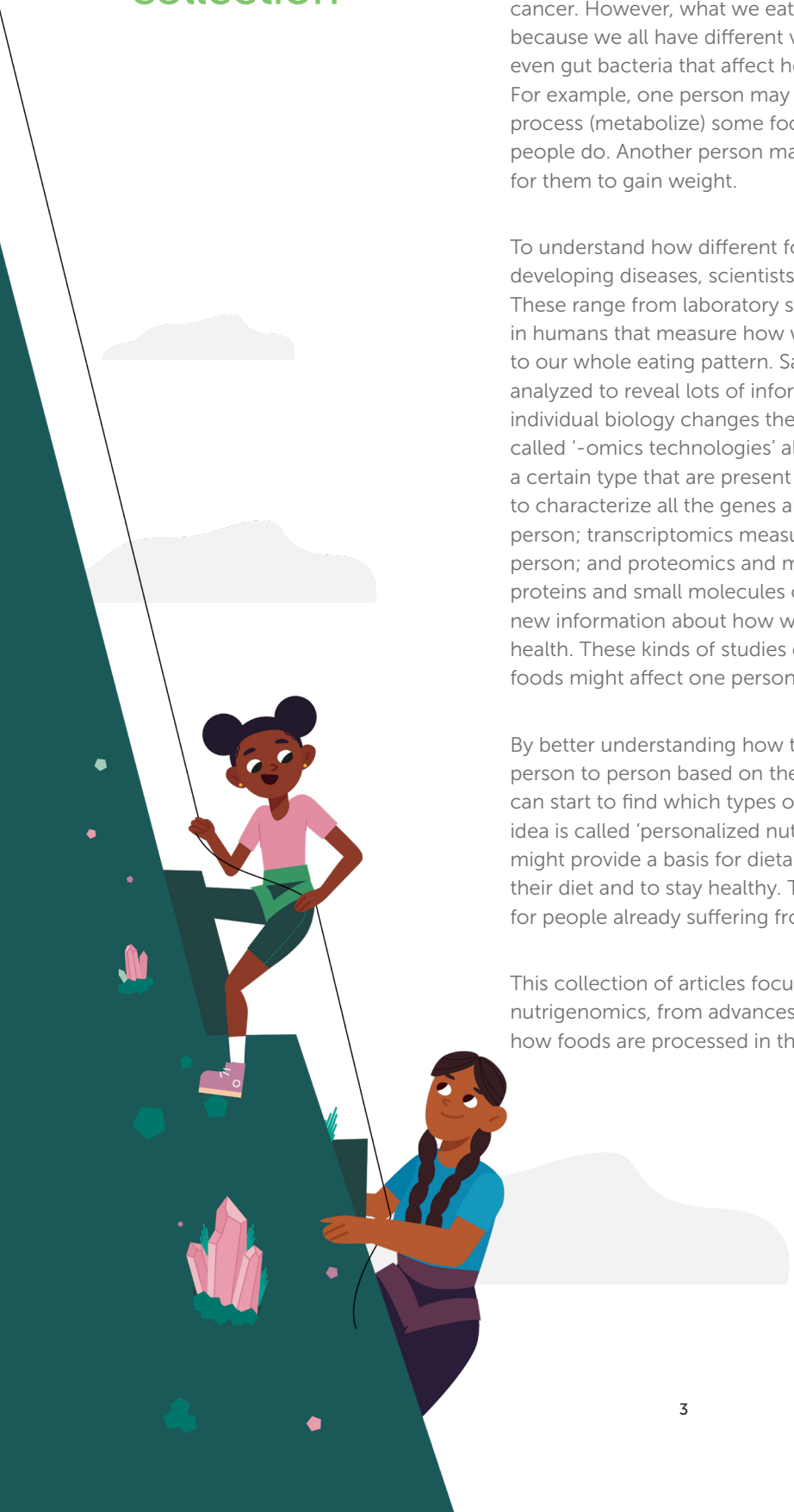
About this collection

What we eat affects our bodies in many different ways. From changing our shape and size, to giving us the fuel to run. From keeping our hair and skin looking good, to affecting our risk of developing diseases like diabetes or cancer. However, what we eat can also affect each of us differently. This is because we all have different versions of genes, molecular regulators and even gut bacteria that affect how we respond to the foods that we eat. For example, one person may have versions of genes that means that they process (metabolize) some food components differently from how other people do. Another person may have versions of genes that make it easier for them to gain weight.

To understand how different foods affect our health and our risk of developing diseases, scientists use many different types of experiments. These range from laboratory studies in cells to studies carried out directly in humans that measure how we react to specific nutrients and foods, or to our whole eating pattern. Samples of blood, saliva and urine can be analyzed to reveal lots of information about how each person's DNA and individual biology changes the way food affects their health. New methods called '-omics technologies' allow us to quickly measure all molecules of a certain type that are present in a sample. For example, genomics is used to characterize all the genes and different versions of genes in a particular person; transcriptomics measures all the genes that are switched on in that person; and proteomics and metabolomics measure the corresponding proteins and small molecules or metabolites. This gives us a huge amount of new information about how what a person eats affects their metabolism and health. These kinds of studies can also help us to understand why particular foods might affect one person differently from another.

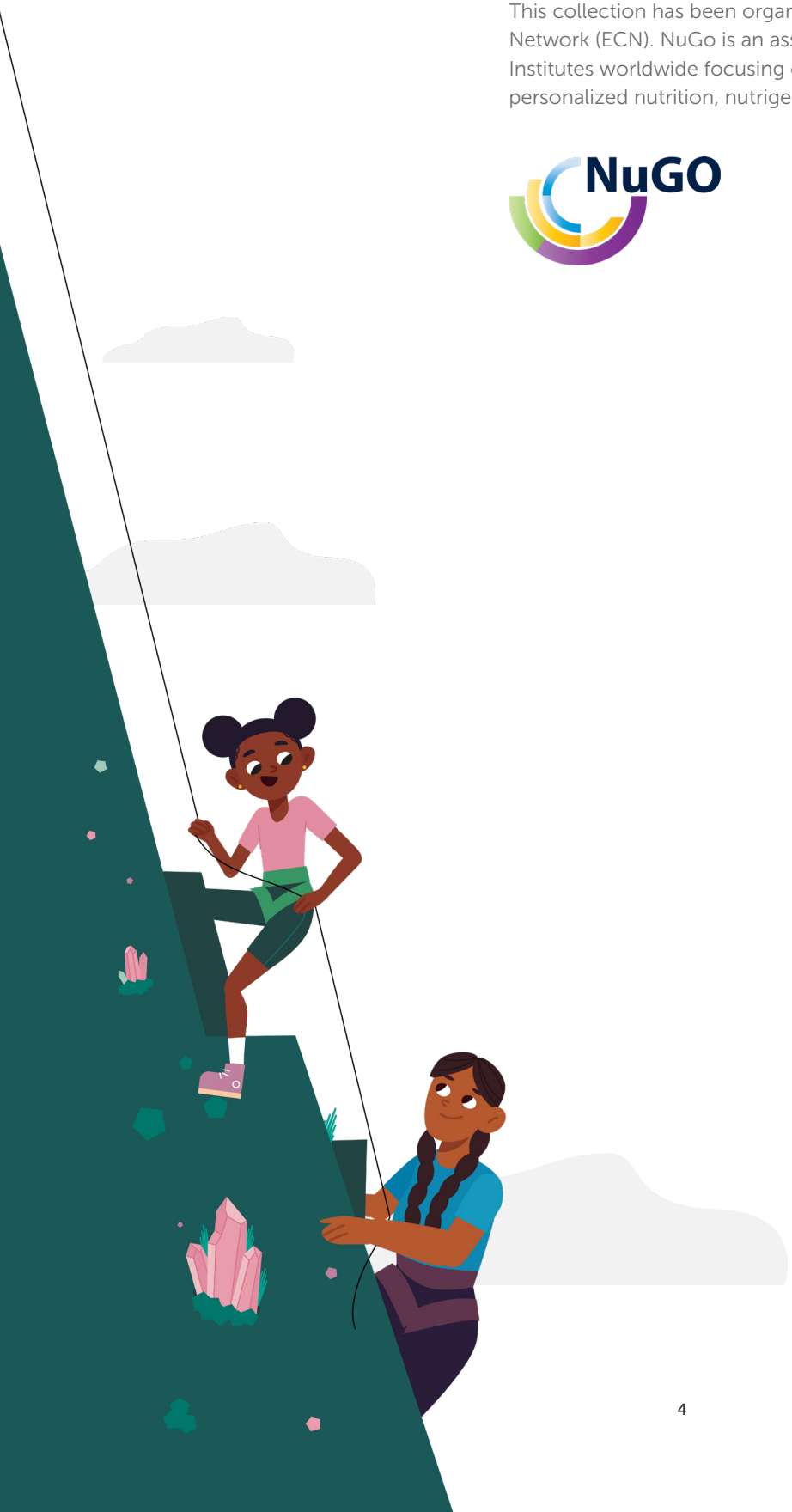
By better understanding how the effects of foods and nutrients change from person to person based on their DNA and other molecular regulators, we can start to find which types of diets may be better for different people. This idea is called 'personalized nutrition'. For example, personalized nutrition might provide a basis for dietary advice to help individual people improve their diet and to stay healthy. This approach might also help find the best diet for people already suffering from a disease that is affected by diet.

This collection of articles focuses on the latest research in the field of nutrigenomics, from advances in technologies used for this research, to how foods are processed in the body and what this means for our health.



At the core of the collection is the application of nutrigenomics as a basis to personalize nutritional advice for individuals and at a public health level.

This collection has been organized by NuGO and the NuGO Early Career Network (ECN). NuGo is an association of Universities and Research Institutes worldwide focusing on research on molecular nutrition, personalized nutrition, nutrigenomics and nutritional systems biology.



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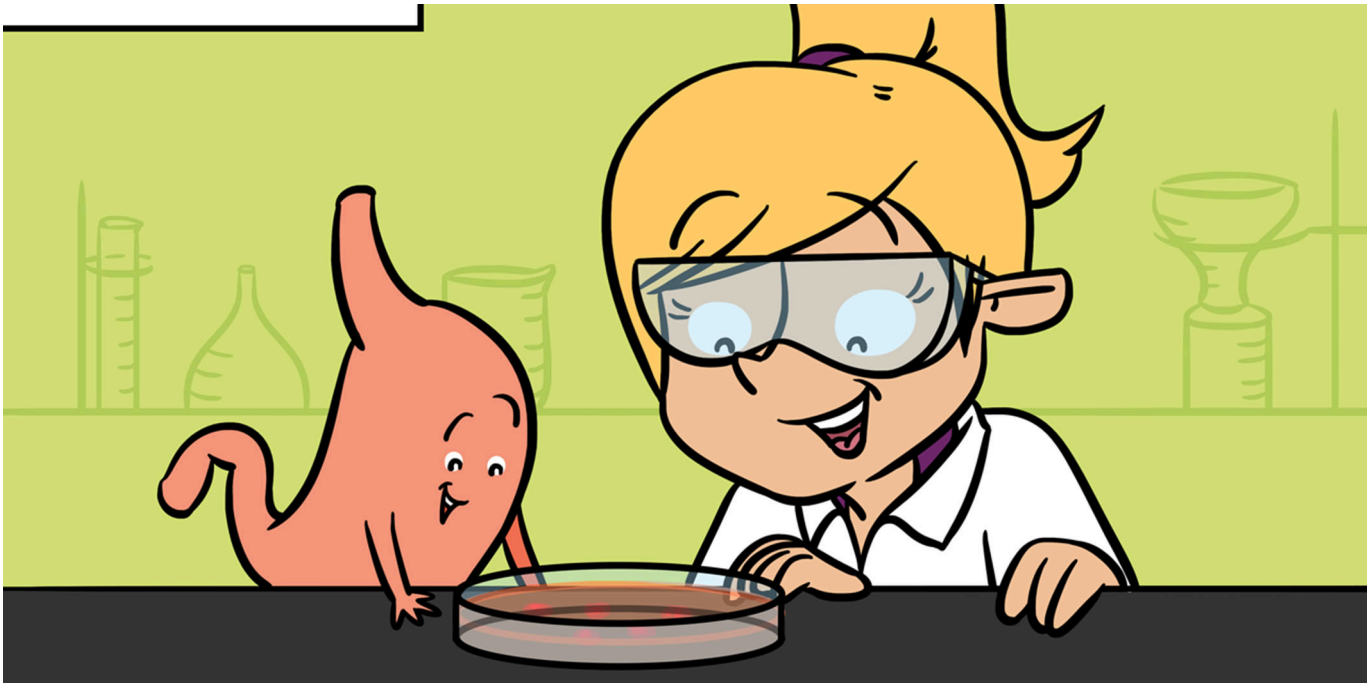

ORGANOIDS—MINI GUTS HELP ANSWER BIG QUESTIONS ABOUT INTESTINAL NUTRIENT TRANSPORT

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Eating healthy foods supplies your body with nutrients to stay strong. But did you ever wonder how nutrients enter your body? After chewing and swallowing, your food is digested, and enters the gut as mush. If you picture your intestine as a tube, the food is on the inside and your body is around the tube. The inner layer of the tube that touches the food is formed by special cells that can transport nutrients like sugar and protein. Some people cannot properly absorb nutrients. The molecules that transport nutrients also transport certain drugs. Thus, investigating intestinal transport is very important to help people with absorption issues and to design better drugs. We used a new scientific model called organoids to study intestinal transport processes. Organoids are tiny "mini-guts" grown in the lab from human cells. Organoids have many advantages over other models used by scientists to study the gut.

HOW DO NUTRIENTS ENTER THE BODY?

When you eat, the food enters your **gastrointestinal (GI) tract** through your mouth and esophagus (Figure 1). The word "gastrointestinal" comes from "gastro", which means "stomach" and "intestinal" which refers to the small and large intestine. Within the GI tract, digestion takes place. Digestion is an important process that breaks down food into parts small enough for your body to absorb. Carbohydrates, proteins, fats, vitamins, minerals, and water are the nutrients contained in things you eat and drink. From these nutrients, your body gets energy and building blocks so that it can grow and function properly. Your body does two things to digest food. First, your teeth crush the food and the GI tract pummels and churns the food mush using its muscles. This is called mechanical digestion. Second, your body produces **digestive juices** to break down the food chemically (Box 1). Even though digestion starts in the mouth, nutrient absorption mainly happens in the small intestine. Compared to the large intestine, or colon, the small intestine is not small, but narrow. While the "large" intestine measures ~ 1.5 meters in an adult, the small intestine is up to 7 m long! If the entire GI tract was spread flat, it would have a surface area comparable to that of a boxing ring (30–40 m^2). This large surface area helps the body absorb nutrients efficiently [1]. To create such a big surface area without taking up too much space in the body, the small intestine is loopy and has numerous folds. These big folds are covered by smaller "valleys" called crypts, and tiny, finger-like projections called **villi**. Hundreds of thousands of villi cover the small intestine and give it the look and feel of velvet. Villi act like a comb that grabs nutrients from the passing food mush. The cells that cover the surfaces of crypts and villi are called intestinal epithelial cells (IECs), and they are the actual sites of nutrient absorption (Figure 1). Like every other cell in the body, IECs are surrounded by a cell membrane. All nutrients need to cross the membrane to be absorbed.

GASTROINTESTINAL (GI) TRACT

A long, twisting tube of joined hollow organs: mouth, esophagus, stomach, small intestine, large intestine, and anus. Together with the liver, gall bladder, and pancreas, which produce digestive juices, the GI tract forms the digestive system.

DIGESTIVE JUICES

For example saliva, stomach acid, and bile. Chemically (acid and denaturation) and physically (bile and emulsification) break down nutrients and contain enzymes (saliva and pancreatic fluids) to split carbohydrates, proteins, and fat.

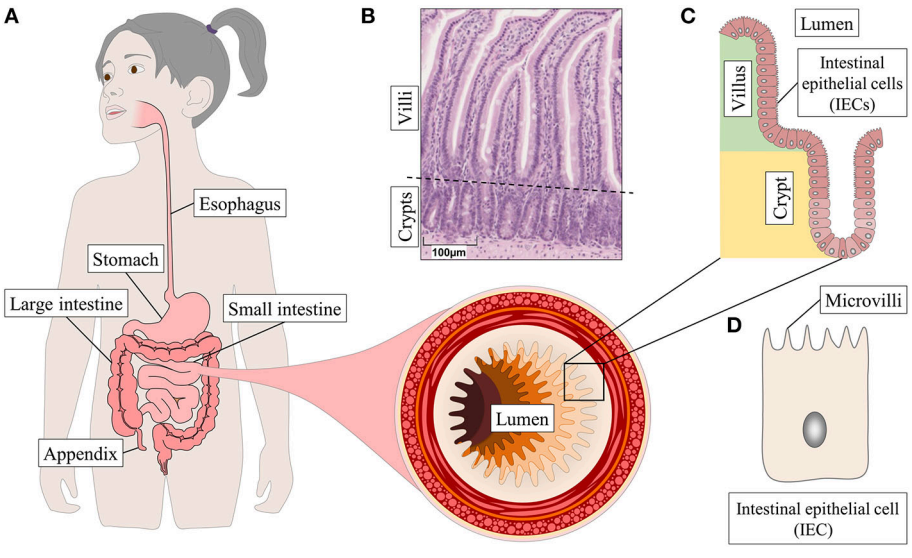

Figure 1

(A) The gastrointestinal tract. A huge surface area is important for an efficient nutrient absorption. To have the largest possible surface area, the small intestine has big folds that are covered with microscopic fingers" (villi) and "valleys" (crypts). **(B)** Photo of an intestinal tissue section. **(C)** Schematic drawing of the crypt-villus structure of the small intestine. **(D)** The cells that make up the inner surface of the small intestine are called intestinal epithelial cells. These cells also have tiny projections, called microvilli that look like hairs and further increase the surface area.

Box 1 | Experiment - digestion starts in your mouth.

The saliva in your mouth is an example of a digestive juice. You can do a simple experiment to test the enzymes in your saliva. First, you eat a bite of bread (without butter or anything else). Then you thoroughly chew it and keep it in your mouth for a while. It will taste a little bit sweet. Why? Because bread contains starch, which is a carbohydrate. Chemically, carbohydrates like starch are long chains of sugar molecules. They do not taste sweet though, as the sweet taste receptors on your tongue only recognize carbohydrates made of one or two sugar molecules. When the enzymes in your saliva break down the long carbohydrate chains into smaller pieces in your mouth, small sugar molecules are generated that activate the sweet taste receptors, and your tongue tells the brain you ate something sweet.

VILLUS/VILLI/ MICROVILLI

Villus: A microscopic, finger-like projection into the lumen made of IECs. Villi: Plural of villus. Microvilli are hair-like structures on the luminal side of IECs, enlarging IEC surface for absorption.

Digestion breaks down carbohydrates into sugars, proteins into amino acids and fat into tiny droplets called micelles, which contain lipids (Figure 2). IECs take up all these small nutrient components. While micelles can go directly through the cell membrane, sugars, amino acids, and vitamins need special molecules called transporters to enter IECs (Figure 2).

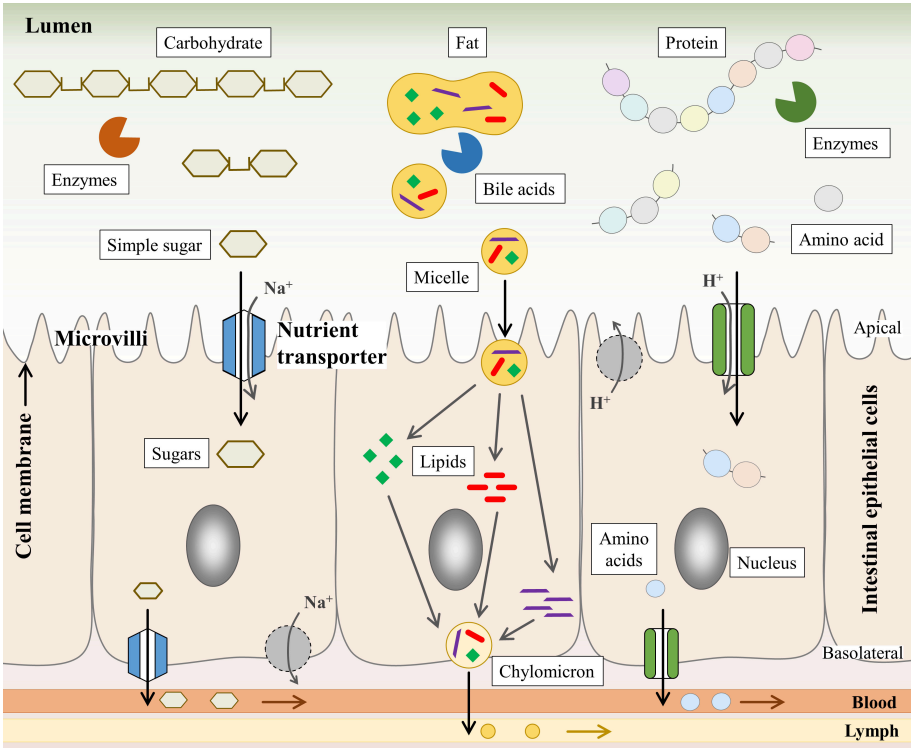

Figure 2

The aim of digestion is to break nutrients down into small parts that can be absorbed by intestinal epithelial cells. Enzymes break up the chains of sugars and amino acids that build carbohydrates and proteins, respectively. Bile acids act as emulsifiers, like soap, they split fat into tiny droplets, called micelles that can be absorbed directly. Lipids are disassembled in the IECs and re-assembled into chylomicrons. Other nutrients move through the cells using "tunnels," called transporters. After passing through the IECs, nutrients are distributed throughout the body *via* the blood and lymph fluid.

WHAT ARE NUTRIENT TRANSPORTERS?

Transporters form little pores or tunnels in the cell membrane, creating doors through which nutrients can pass. The inner side of the intestine that contains the food mush is called lumen. For absorption, transporters sit on the cell membrane facing the lumen. The reason

why nutrients take these doors to leave the lumen and enter the cell is because of diffusion. Diffusion describes a process where molecules move from an area of high concentration (e.g., you ate a muffin and now a lot of sugar is in your intestinal lumen) to an area of low concentration (fewer sugar molecules are in your IECs). The bigger the difference in concentrations, the bigger the physical force that draws the molecules into the cells. Some transporters move ions in parallel to nutrients, using the concentration difference of the ions to fuel nutrient transport. Ions are electrically charged particles, for example salt contains positive sodium and negative chloride ions. But why does the transport of nutrients not slow down or stop? Due to continuous transport, you would expect a decrease in the concentration difference or even the same concentration in the lumen and inside the IECs. To prevent a stop of nutrient transport, IECs also have transporters on their opposite side or "basolateral" side. Using energy, these transporters "pump" out ions, maintaining the low concentration inside the IECs needed for nutrient absorption. Furthermore, nutrient transporters on the basolateral side help nutrients to leave the IECs, so they don't get overloaded with nutrients. Sugars, amino acids, and vitamins thus pass through the IECs and into the blood stream with the help of transporters. In contrast, fat passes right through the cell membrane, not needing special transporters to do so. Micelles are split into their components in IECs, reassembled into lipid-transport particles called chylomicrons, and are released from IECs into the **lymph**. All nutrient are then distributed throughout the body and used by all its cells (Figure 2).

LYMPH

A colorless fluid that is formed when blood fluid (called plasma) exits blood vessels. Fat from the intestines and immune cells travel with the lymph. The main lymph vessel merges with a big blood vessel in the chest, and lymph and blood are blended again.

WHY DO WE NEED TO STUDY NUTRIENT TRANSPORT?

As you can imagine, nutrient absorption and transport are very complicated processes. Many types of transporters exist that are specific for different types of nutrients, and there are even different transporters for particular types of amino acids and sugars. Also, certain transporters can move more than one type of sugar, and sometimes several types of transporters can move the same nutrient. So, it is no wonder that nutrient absorption is still not fully understood. It is very important to study nutrient transport, because there are diseases that are caused by defective transporters, and some patients have normal transporters but still cannot absorb certain nutrients. For example, patients with fructose-malabsorption, who cannot absorb fruit sugar, often have a functional fructose transporter. Knowing what is wrong in each of these cases could help scientists to find treatments. Treatments are important because malabsorption can cause health problems like severe stomachaches.

Nutrient transporters are also important in drug development, because some medicines are taken up by nutrient transporters. For example, certain antibiotics used to fight bacterial infections are taken up by nutrient transporters, because these drugs have chemical structures

similar to small peptides. If we knew the exact details of transport processes, we could invent drugs that can be very efficiently absorbed and cause fewer side effects.

HOW IS NUTRIENT TRANSPORT STUDIED?

Unfortunately, it is difficult to study nutrient transport. Scientists study nutrient transport using what are called **biological models**, because we cannot investigate transport processes directly in the human intestine. Normally, scientists use either **cell lines** or animals as models, but both have huge drawbacks. Cell lines need to grow and divide constantly so that they will stay alive long enough for the experiment. Therefore, most cell lines originate from tumors or have had their DNA altered. But the changes that make these cells grow so well also change other properties. In particular tumor cell lines, that are very often used to investigate intestinal nutrient transport, sometimes have more transporters than normal cells, or fewer, or they can even lack certain transporters.

BIOLOGICAL MODEL

Experimental systems that represent tissue functions or diseases in a simplified way. Models respond to medical tests similar to the natural tissue and provide insight into complex biological functions.

CELL LINE

Cells of plants, animals, or humans grown in small plastic containers and used as biological models. They "swim" in medium, a liquid that contains everything the cells need to live and grow.

On the other hand, in animals you can study more than just absorption of nutrients by IECs. Nutrient uptake can be influenced by factors like the composition of food, the speed with which the food mush passes the villi, and how fast nutrients are passed on to the blood on the basolateral side. This is why it is important to consider the whole organism and not just certain cells. However, if you think of a mouse, the most common animal model—they are rodents, they eat completely different from humans, and their GI tract has a different structure. And even though nutrient transporters of mice and human are similar, they are not the same. Nonetheless, scientists used these models for years, until... a new, groundbreaking method was developed, intestinal organoid culture!

WHAT ARE ORGANOIDS?

Organoids are small, organ-like structures made of cells. They do not grow as a "cell-lawn" like normal cell lines do, they grow into 3D structures in a substance that resembles jello. Intestinal organoids are like "mini-guts" and they can be grown from crypts (Figure 3) [2]. As the crypts grow in the culture dish, they close and form a balloon, with the IECs forming the wall of the balloon that faces a central lumen, which is like the air inside the balloon. Over time, the organoid balloon starts budding and develops to an octopus-like shape. The numerous arms of the octopus and the areas in between are like the crypts and villi of the small intestine (Figure 3).

Only very small pieces of intestinal tissue are necessary to get enough crypts to grow organoids. How do we get them? There are two options. Sometimes patients need surgery to have parts of their

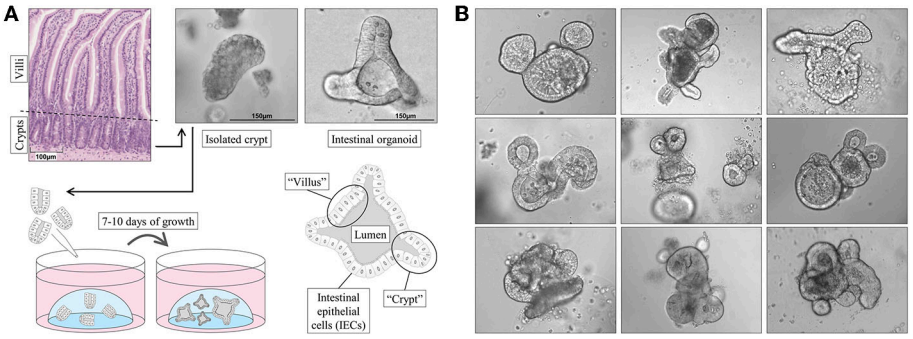

Figure 3

Figure 3

(A) Intestinal organoids can be grown from isolated crypts in 7–10 days. These "mini-guts" are made of IECs and are a great tool for research. They range in size from the width of a hair (100 µm) up to more than 2 mm, and are visible as small dots even without a microscope. **(B)** Organoids are also beautiful. Sometimes, if you look through the microscope it seems that they are looking back at you. Organoids can have all kinds of shapes. With a little bit of imagination, you can find a lot in your petri dish! What do you see?

intestines removed, mainly because of intestinal inflammation or cancer. In these cases, some of the healthy tissue next to the damaged part is removed, too. This tissue can be used to obtain crypts. Biopsies are the other option. A biopsy is a small piece of tissue that can be taken from the GI tract during a medical examination. Biopsies are taken using small clamps that bite into the intestinal wall to get tissue pieces of $\sim 10\ mm^2$. To compare, a stud from a LEGO brick has an area of $18\ mm^2$. Out of 2–3 of these tissue pieces, we can obtain 150–300 crypts, which is enough to start growing intestinal organoids [3].

WHY ARE ORGANOIDS SUCH A GREAT MODEL?

Organoids have many advantages:

- they consist of IECs that are exactly like those in the intestine.
- unlike cell lines, they do not originate from cancer or have their DNA altered.
- they are of human origin and not from animals such as mice.
- they can be grown from various parts of the intestine—this is important, because some nutrients are only taken up in certain areas of the intestine, and the necessary transporters are only found in those intestinal areas.
- they can be grown from individual patients and used to find the best treatment for each specific patient. This is called "**personalized medicine**."

PERSONALIZED MEDICINE

The same disease (symptoms) can have different causes. Personalized medicine takes this into account and matches the treatment to each patient individually, to have the best possible treatment.

CONCLUSION AND OUTLOOK

There is still a lot to explore about nutrient absorption in the GI tract. Intestinal organoids are a great tool for this area of research and they will help scientists to better understand diseases like nutrient malabsorption. Using human intestinal organoids as a model system, we now have a better way to test drug absorption through nutrient transporters, which helps with drug development. Last but not least, intestinal organoids will save the lives of laboratory animals, because

using human organoids for experiments will reduce the number of experiments performed on animals.

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ORIGINAL SOURCE ARTICLE

Zietek, T., Giesbertz, P., Ewers, M., Reichart, F., Weinmüller, M., Urbauer, E., et al. 2020. Organoids to study intestinal nutrient transport, drug uptake and metabolism—Update to the human model and expansion of applications. *Front. Bioeng. Biotechnol.* 5:577656. doi: 10.3389/fbioe.2020.577656

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ARASI, AGE: 8 YEARS

Hola Amigo! I am Arasi. I am in 3rd grade. I love to dance, play the piano, and draw! In my free time, I read books, my favorite series are diary of a wimpy kid and dork diaries. My favorite colors are pastel pink, purple, and mint green. When I grow up, I want to become a lawyer. I just want to say, for a better world, kindness is the way to go! Addios!

HANIYEH, AGE: 14 YEARS

Hello, I am Haniyeh! My favorite subjects in school are Art and English, and like drawing and mixing/mastering in my free time. I enjoy reading about various topics on the internet, and am fascinated with analysing mysteries and strange events.

AUTHORS

TAMARA ZIETEK

Tamara Zietek holds a Ph.D. in biochemistry and worked at the chair for Nutritional Physiology at the Technical University of Munich. During her time there, she studied nutrient transport, drug absorption, and hormone production in the intestine. While they were working in the same building, Tamara and Eva met by chance, and they combined intestinal organoids and methods for measuring nutrient transport. Tamara currently works for an organization that promotes human-based, animal-free technologies, and strives to save animal lives.

EVA RATH

Eva Rath studied "Nutrition and Biomedicine" and now works as a *post-doc* at the chair for Nutrition and Immunology at the Technical University of Munich. The topic of her research is intestinal epithelial cells and how the cellular metabolism is altered when the intestine gets inflamed. Since 2013 she has worked with intestinal organoids and she is still amazed by the shapes they grow into and fascinated by the research possibilities they offer. Tamara and Eva first teamed up in 2013 and have been colleagues and friends ever since. *eva.rath@tum.de

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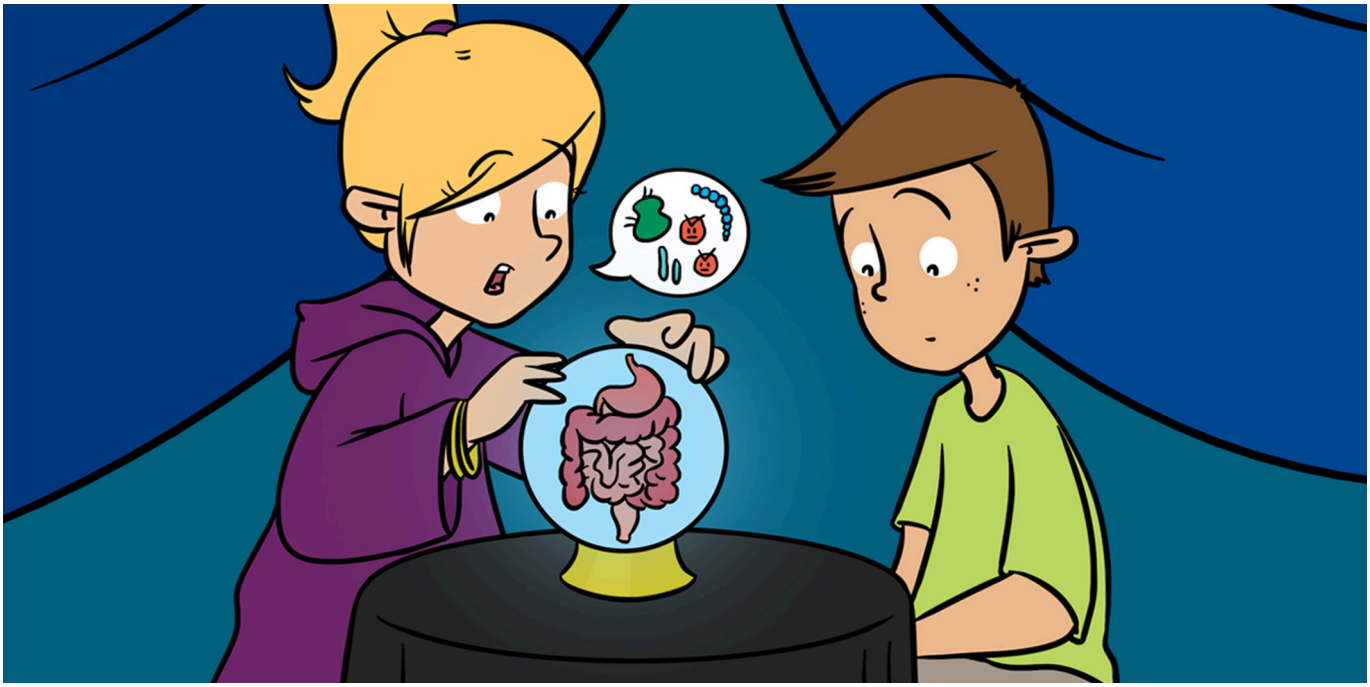

THROUGH A CRYSTAL BALL: USING BACTERIAL SIGNATURES TO PREDICT INTESTINAL DISEASES

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MARGARIDA
AGE: 10

Each of us has a mix of microbes that colonizes our intestines, as unique as our fingerprints. Most microbes are beneficial and are essential for keeping us healthy. If the microbes in our intestines are out of balance and too many harmful microbes take control, intestinal diseases might result. Recent advances in computers and laboratory methods have helped scientists understand much more about our intestinal microbes and their unique signatures: who they are, what they do, and which useful or harmful substances they produce. We wanted to know which bacteria can cause intestinal diseases, and whether we could use these bacterial signatures to foresee the futures of patients. We analyzed the bacteria in patients with intestinal diseases and identified certain bacteria that can produce harmful compounds. This information could help doctors predict who is more at risk of developing intestinal disease and which treatment could work best for each patient.

YOUR MICROBES—YOUR IDENTITY

GUT MICROBIOTA

The group of microorganisms that live in human intestines. Most of the organisms are beneficial and perform functions that keep us healthy.

Microbes are tiny creatures that are impossible to see without a microscope. Trillions of microbes live in and on our bodies, especially in our intestines. The **gut microbiota** is the term we use to describe this entire vast and diverse collection of bacteria and other organisms that live in our intestines. Unfortunately, we mostly associate bacteria with illness. However, most of the bacteria in our bodies are beneficial to human health. They help us break down and digest the foods we eat, produce essential vitamins, and fight off harmful bacteria. In return, we offer them a place to live and the nutrients they need to thrive. Beneficial bacteria are also important to create a powerful immune system. The immune system protects our bodies against illnesses. When the number of harmful bacteria is kept to a minimum, they generally do not cause problems. But under certain conditions, harmful bacteria can multiply and kick out beneficial bacteria, which can result in multiple diseases [1].

Is everyone's gut microbiota the same? Yes and no! While one-third of the gut microbiota is common between individuals, two-thirds of each person's microbiota is unique to them and as personal as their fingerprints! While everyone's gut microbiota performs similar functions, these functions are not necessarily carried out by the same bacteria in everyone's body [2]. You could think of the intestines as a city for microbes. Every city has its own firefighters, police officers, bus drivers and garbage collectors. Different people perform these roles in each city and within each city, those people can change over time. In the bacterial world, hundreds of microorganisms can perform essential roles such as producing vitamins or breaking down the carbohydrates in the foods we eat [3]. This means that, even if our bacterial communities look different, they are doing the same set of important jobs. In a city, if many productive residents live there and if they can perform multiple essential jobs, the city will flourish. Similarly, we are healthier if our intestines are home to a high number of beneficial bacteria that can perform a variety of functions (Figure 1).

THE CONNECTION BETWEEN GUT BACTERIA AND CROHN'S DISEASE

Scientists have been studying whether changes to our intestinal bacteria are somehow linked to the foods we eat, the medications we take, or to whether we are healthy or sick. We were particularly interested in understanding whether the bacteria that live inside people who have long-lasting intestinal inflammation (also called Crohn's disease) have unique and harmful characteristics. Crohn's disease was named after the doctor who first described it in 1932, and it affects millions of people worldwide. Crohn's disease affects teens and young adults, but mostly people 20–40 years of age. In Crohn's

Figure 1

Trillions of bacteria live in and on our bodies. Most of them live in our intestines. To stay healthy, we need a wide range of bacteria that can perform many functions essential for our health. It is important for the number of beneficial bacteria to remain higher than the number of harmful ones. In patients with intestinal diseases, fewer bacteria live in their intestines and harmful bacteria take over and produce toxic substances that lead to disease.

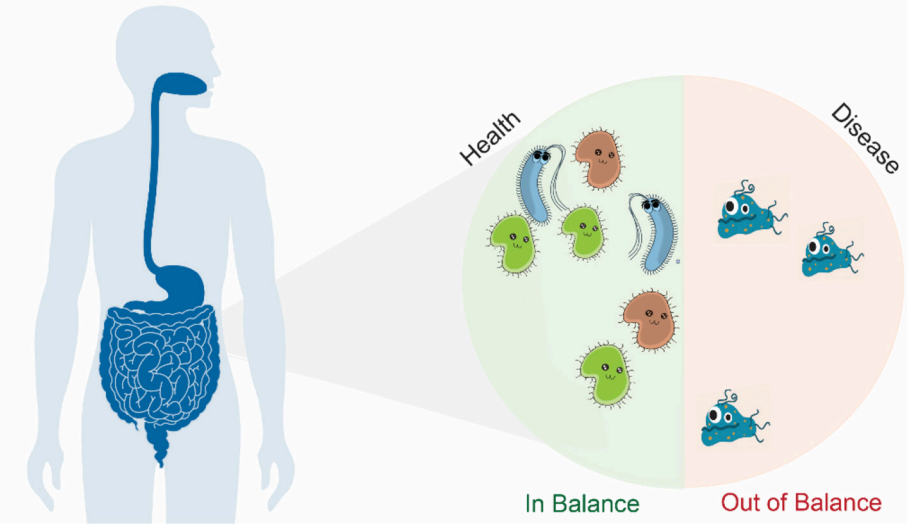

Figure 1

disease, parts of the intestine become red and swollen. Patients can have times when they get very sick (what we call **flare-ups**) and other periods when they feel completely fine (what we call **remission**). Patients with Crohn's disease suffer from bloody diarrhea, abdominal pain, weight loss, fever, and loss of appetite.

FLARE-UPS

Periods of time when a patient with a long-lasting disease shows more symptoms and feels worse.

REMISSION

Periods of time when a patient with a long-lasting disease shows no symptoms and feels better.

Normally, the immune system watches out for danger. However, in Crohn's disease, the immune system gets confused and attacks both the good and the bad bacteria. Disturbing this bacterial balance increases the toxins produced by harmful bacteria and causes destruction of the intestinal tissue. Medicines can help reduce the immune system attacks, but intestinal tissue damage gets worse over time. Research showed that patients with Crohn's disease have bacterial communities that look quite different from those found in healthy individuals. These bacterial communities were mostly dominated by bacteria with the potential to become harmful under certain conditions.

WHO IS THERE? WHAT ARE THEY DOING?

BACTERIAL SIGNATURE

Unique patterns of bacterial community composition and function that can differentiate between physiological and pathological conditions and can be used to predict the risk of disease development or progression.

To figure out which bacteria are causing Crohn's disease, we asked patients to collect stool samples (poop) during both remission and flare-ups. We performed laboratory experiments to measure the molecules and compounds present in the poop samples. We also broke open the bacterial cells to release the DNA so we could analyze the bacterial genes and identify which bacteria were present. Finally, we used computers and statistics to understand the relationships between the bacteria, their products, and the health status of patients. All of this information gives us specific patterns, called **bacterial signatures** [4, 5], for remission and flare-ups (Figure 2).

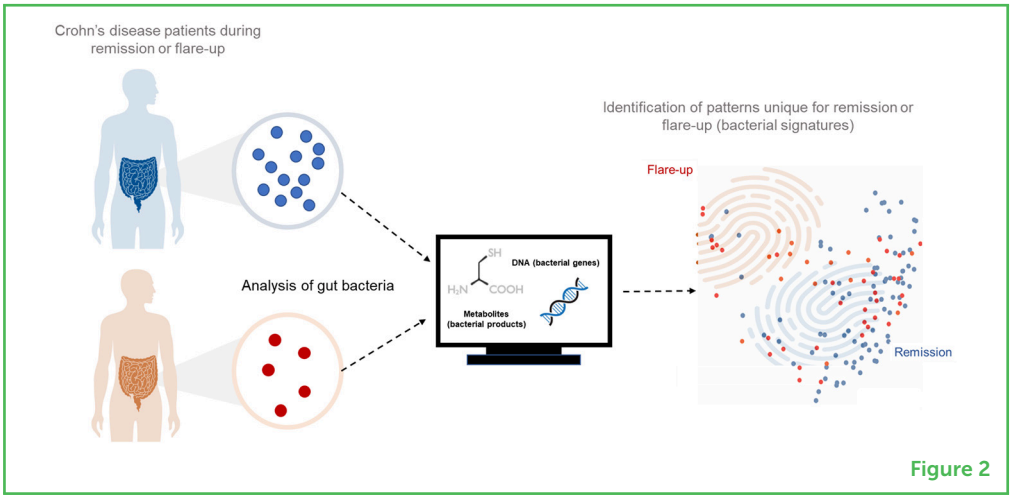

Figure 2

We took samples of intestinal bacteria from Crohn's disease patients who were either in remission or experiencing flare-ups. We did experiments to determine which metabolites were being made by the bacteria and we broke open the bacterial cells to study their genes. We analyzed all the data using computers and mathematics. In the end, we could see unique patterns, which we called bacterial signatures, for each condition.

We found a big difference in the numbers of microbes in the intestines of patients during periods of remission vs. flare-ups. Many more bacteria were present during remission, and they were also much more diverse, meaning there were more types of bacteria present. In addition, we saw big changes in the numbers of specific types of microbes between these two groups. For example, there were more bacteria from the groups *Escherichia coli* and *Desulfovibrio* during flare-ups. To learn more about these bacteria, we measured the concentration of the **metabolites** they produce. Metabolites are small molecules that take part in, or are produced by, the chemical reactions of metabolism. The concentrations of certain metabolites in poop, urine, or blood are linked to the risk of developing certain diseases. When we compared patient samples from remission vs. flare-ups, we found differing amounts of certain metabolites.

METABOLITES

Small chemical compounds that are involved in or produced by an organism's metabolism. In this research, we looked at metabolites produced by bacteria.

TEACHING COMPUTERS TO TELL THE FUTURE

Next, we wondered if we could predict whether patients with Crohn's disease would remain in remission or have flare-ups, based on their bacterial signatures. To do so, we used **machine learning**, in which computers are trained to perform complex tasks. For a computer to identify the bacterial signature of a patient who will soon get a flare-up, the computer is given many examples of bacterial signatures from patients during flare-ups, so that the computer learns the patterns of what a flare-up bacterial signature looks like. This phase is called learning. Then, we test the computer on what it learnt by challenging it with examples of bacterial signatures where the computer needs to decide whether each signature came from a healthy subject or a patient having a flare-up. This phase is called testing. If the model passes our tests, we can rely on it to tell whether a patient is healthy or will soon have a flare-up from the bacterial signature. This phase is called prediction. To our excitement, our computer was correct in its prediction of flare-ups 96% of the time (Figure 3)!

MACHINE LEARNING

A branch of science which allows computers to perform tasks without us having to tell the computer how to do it. The computer learns to perform a task by observing a lot of examples and trying to figure out how to make the best judgement.

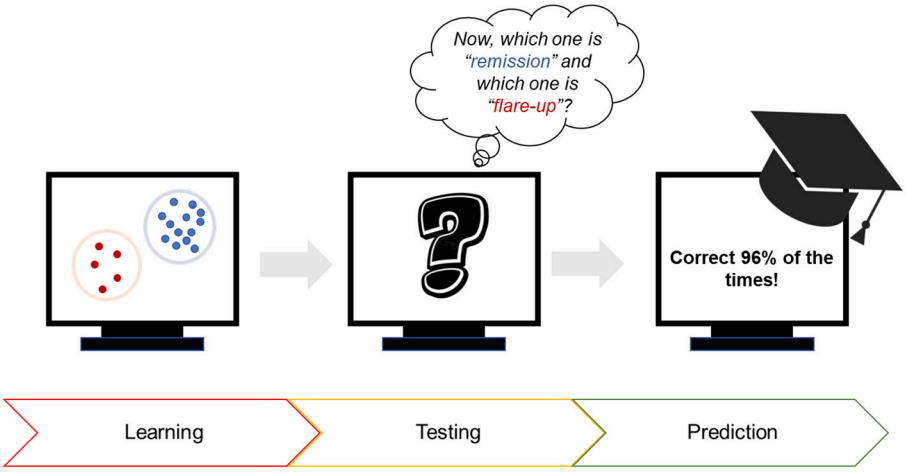

Figure 3

Using computers to predict the occurrence of flare-ups in Crohn's disease patients. First, the computer was shown many bacterial signatures of patients during flare-ups. Then, the computer was tested to see if it could identify known signatures as "remission" or "flare-up." Third, we used the computer to predict whether a patient was about to experience a flare-up. The computer was correct 96% of the time!

MICROBIAL TREATMENTS FOR INTESTINAL DISEASE

Our research could be useful for treating patients with intestinal diseases like Crohn's disease. If we can use machine learning to analyse bacterial signatures in patients' poop, this could help us tell whether the patient is healthy or might develop intestinal disease in the future. If we can identify the exact types of bacteria that are decreasing when a patient has a flare-up, we might be able to collect those bacteria, let them grow and multiply in the lab, and make them into a pill that we can give to patients to help them improve. Such beneficial bacteria are called **probiotics**. We all have some probiotic bacteria in our intestines, but they are also found in foods including yogurt, cheese, bread, or buttermilk.

PROBIOTICS

A group of beneficial bacteria that people can consume to restore balance to their gut bacteria.

If healthy people have enough beneficial microbes, they can donate poop samples that we could then transfer into the colons of patients with poor bacterial signatures. This is called **fecal microbiota transplantation**. Transplanting the healthy microbes into patients could kick-start the bacterial community and restore balance to the gut microbes. There is still some work to do before we can effectively treat patients using the information from our study. The work we have done so far is already important because the more we know about gut bacteria and their functions, the more likely we will be to find new, effective treatment options for the millions patients across the globe who suffer from intestinal diseases like Crohn's disease.

FECAL MICROBIOTA TRANSPLANTATION

A procedure in which poop from a healthy donor is transplanted in the colon of a patient. The good bacteria replace the bad ones, and a healthy balance is restored.

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ORIGINAL SOURCE ARTICLE

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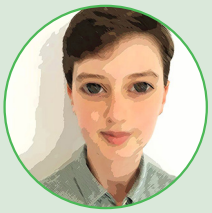
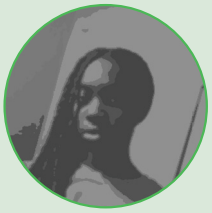
YOUNG REVIEWERS



ALASTAIR, AGE: 14
I like to tweak computers. I am interested in everything STEM-related.



AYA, AGE: 14
Aya is a 14 years old who loves Biology, especially anything related to cells. She also loves books, sci-fi, and R&B. Outside of school, she spends her time reading, playing volleyball, and exploring molecular biology!

JAMES, AGE: 12
I am a big supporter of environmental conservation. My favorite animals are the rhino and pandas, particularly red pandas.

LUISA, AGE: 12
My name is Luisa and I am 12 years old. I like painting/drawing, especially people. I also really like volleyball and hanging out with my friends. My favorite foods are sushi, ramen, and lasagna. My favorite animals are squirrels, cats, and butterflies. The colors I like the most are brown, green, and black. Because my mum is a nutritionist, I have grown to hear about good and bad bacteria in food quite a lot, so I am familiar with healthy food.

MARGARIDA, AGE: 10
My name is Margarida and I am 10 years old. I like acting and drawing clothes. I also like horses, dogs, cats, and to watch mushrooms and herbs in nature! My favorite foods are sushi, ramen, and spageti. I love to cook breakfast for my mum and sister ☺. Pancakes are my speciality! My mum is a nutritionist, so I hear a lot about good bacteria and food that protects them!

AUTHORS

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DO ALL PEOPLE WITH OBESITY HAVE INCREASED RISK OF DISEASE?

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[2] *Department of Nutrition, Faculty of Medicine, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway*

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YOUNG REVIEWERS:

HRISHIKA
AGE: 13

PRIYANKA
AGE: 13

Our cells use the food we eat to produce the energy needed to do work. This amazing process is called metabolism and it is necessary for survival. If we eat more than we need, we will gain weight and may become obese. Obesity affects how cells and organs perform work and also increases the risk of metabolic diseases, which include type 2 diabetes and cardiovascular diseases. Metabolic diseases are the most common diseases of our time. National and global health authorities are working hard to prevent and treat obesity and obesity-related diseases. However, some people with obesity appear to have *normal* metabolism. Why do some obese people develop metabolic diseases while others do not? In this article, we discuss how metabolism may differ in people with obesity. We also describe some key reasons why some people with obesity may be healthier than others.

METABOLIC REGULATION IS NECESSARY FOR SURVIVAL

METABOLISM

All the work that cells of a living organism perform to stay alive.

The work that the cells of an organism perform to stay alive is called **metabolism**. The energy required for metabolism comes from nutrients in foods that we eat, digest, and absorb into the bloodstream (Figure 1). Carbohydrates, fats, and proteins from foods are energy sources for the body's cells. A healthy diet—including fruits and vegetables, whole grains, and fish—is an important source of nutrients and energy. Together with exercise, a healthy diet will result in a well-regulated metabolism and a reduced risk of certain diseases.

Figure 1

Food is digested in the gut and nutrients, like glucose and fat, are taken up by the blood. The blood transports the nutrients to cells and organs, which use them for energy metabolism. If energy is not needed, the nutrients are converted to fat and stored for later use.

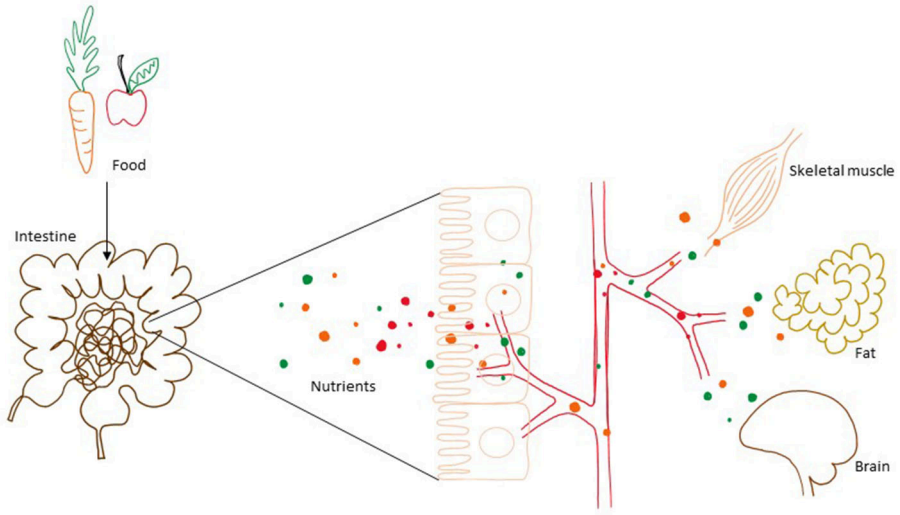

Figure 1

GLUCOSE

A simple sugar molecule (a monosaccharide, a type of carbohydrate). An important energy source for cells, and always found in blood.

Carbohydrates are the most important energy source for the body's cells. Carbohydrates are taken up into the blood from the intestine, in the form of a sugar called **glucose**. The level of glucose in the blood increases after a meal and decreases again when the cells take it up. To fuel our bodies when we are not eating, we also need to *store* metabolic fuels. Fat is the most energy-dense nutrient and is the form in which energy is stored when we take in more food than we currently need for energy.

Metabolism must be carefully regulated so that our bodies can deal with short- and long-term changes in energy availability. This regulation involves communication between various tissues and organs. After a meal, when we start to exercise, or after an overnight fast, the body's organs must be informed about whether energy should be stored or mobilized from storage sites. Much of this communication is done by signaling molecules traveling in the blood, including hormones and metabolites (chemical products of metabolism). The body's ability to store energy as fat is important for survival and allows us to vary our energy intake from day to day. Today,

however, most of us live inactive lives and have an abundance of tasty and energy-dense foods available. Unfortunately, this makes it easy to eat more food than the body needs, leading to increased weight and obesity.

OBESITY IS ELEVATED WEIGHT RELATIVE TO HEIGHT

OBESITY

A body mass index (BMI) of 30 kg/m^2 or more.

BODY MASS INDEX

A measure of excess adiposity. Calculated as a person's weight in kilograms divided by the square of the height in meters: kg/m^2.

All over the world, the number of people with **obesity** has been increasing [1]. The number of children with obesity is also increasing, and during the last 40 years (1975–2016) the number of girls with obesity has increased from 5 to 50 million and the number of boys with obesity has increased 6–74 million [2]. But what is obesity? Obesity is simply when a person's weight is elevated relative to their height. To figure out how elevated a person's weight must be to be considered obese, we must calculate the **body mass index**, or BMI. BMI is the weight in kilograms divided by the square of the height in meters (kg/m^2). Using this measure, people fall into one of four categories: underweight, normal weight, overweight, and obesity. Obesity is defined as a BMI of 30 kg/m^2 or more. Note that, by this definition, a person defined as obese may have a lot of muscle mass. However, most people with obesity have large body-fat stores.

OBESITY INCREASES THE RISK OF METABOLIC DISEASES

METABOLIC DISEASES

An umbrella term for a broad range of diseases affecting metabolism, including obesity, type 2 diabetes, cardiovascular disease.

TYPE 2 DIABETES

A condition in which cells cannot use blood glucose efficiently for energy, so the glucose level in blood gradually gets too high.

CARDIOVASCULAR DISEASE

A general term for conditions affecting the heart or blood vessels, such as heart attack and stroke.

There are two main stores of body fat: underneath the skin, called subcutaneous fat, and surrounding the organs in the abdomen, called visceral fat. The visceral fat stores are the most important for metabolic regulation—if a person's visceral fat stores increase, at some point, their metabolic regulation will be affected and may even be dysfunctional. Over time, a dysfunctional metabolism can lead to **metabolic diseases** such as **type 2 diabetes** and **cardiovascular diseases** [3]. These are the most common diseases of our time, and both national and global health authorities are working to treat and prevent obesity and obesity-related diseases.

Weight reduction will normally improve metabolic regulation and thereby reduce the risk of metabolic diseases. But unfortunately, weight reduction may be difficult to maintain for a long period—often excess weight is regained. To effectively prevent and treat obesity -related diseases, we need more knowledge about how metabolism is affected by obesity.

BIOMARKERS OF HEALTH AND DISEASE

If you have an infection, you often know this because you feel sick and have a fever. Metabolic diseases take years to develop, and

people often do not have obvious symptoms while these diseases are developing. To understand a person's risk for metabolic diseases, blood samples are taken to measure **biomarkers**—substances that indicate the status of metabolism and overall health.

BIOMARKER

A substance that is measured in blood, urine, or another tissue and is used as an indicator of normal or abnormal biological processes.

The amounts of glucose and fat in the blood are carefully regulated as part of normal metabolism. In addition, molecules called fat transporters function to move fat throughout the body *via* the blood. When fat stores increase, so do the amounts of glucose, fat, and fat transporters in the blood. These substances can serve as biomarkers and their levels are therefore used as indicators of health status. There may be many other biomarkers of metabolic regulation that may be discovered as we continue to study the metabolism of people with obesity compared to people with normal weight. Maybe there are markers that can warn us about the risk of metabolic diseases long before they occur!

PEOPLE WITH OBESITY ARE DIVERSE

Although obesity generally increases the risk of developing metabolic diseases, people with obesity are diverse. Some people with obesity are described as *low-risk obesity* meaning, when compared to people with *high-risk obesity*, they have healthier blood fat levels and normal or only slightly affected blood glucose regulation, despite having similar amounts of body fat [4, 5]. Why is this? Could there be undiscovered biomarkers that explain this difference in obesity-related metabolic regulation? Perhaps individuals with low-risk obesity will transition to high-risk obesity with time?

One way to start answering these questions is to study metabolic regulation in people with low-risk and high-risk obesity—and that is what we did. We created a detailed map of many kinds of molecules in the blood that may increase our understanding of metabolic regulation in obesity, to see whether any of those molecules might serve as new biomarkers of health and disease.

CHARACTERISTICS OF INDIVIDUALS WITH LOW-RISK OBESITY

Our study included 30 participants (18 males and 12 females) who were divided into three groups: low-risk obesity, high-risk obesity, and healthy normal weight. Participants were grouped based on BMI and blood levels of fat and glucose. While the low-risk obesity and normal-weight groups had normal levels of fat and glucose in blood, the high-risk obesity group had high blood levels of these biomarkers. In the low-risk obesity group, there were nine participants with a mean age of 49 years and mean BMI of 33 kg/m^2. The high-risk obesity group had 10 participants with a mean age of 52 years and mean BMI of 32

kg/m^2. The normal weight group had 11 participants with a mean age of 47 years and mean BMI of 23 kg/m^2 [6]. To investigate possible new biomarkers for high- and low-risk obesity, we analyzed blood samples for a wide range of metabolites.

We found that the low-risk obesity group had lower levels of various fat transporters in their blood compared to the high-risk obesity group (Figure 2). They also had lower levels of some amino acids—the building blocks of proteins—namely isoleucine, leucine, and valine. The normal-weight group had lower levels of the amino acid phenylalanine compared with the low-risk obesity group. The types of fat found in the blood were more favorable, meaning less of the fat that cause cardiovascular disease, in the low-risk obesity group compared with the high-risk obesity group (Figure 2).

Figure 2

Compared to low-risk obesity, high-risk obesity is characterized by higher blood levels of fat and amino acids, and lower blood levels of "good fat". Compared to low-risk obesity, normal weight is characterized by lower blood levels of fat and unchanged levels of amino acids.

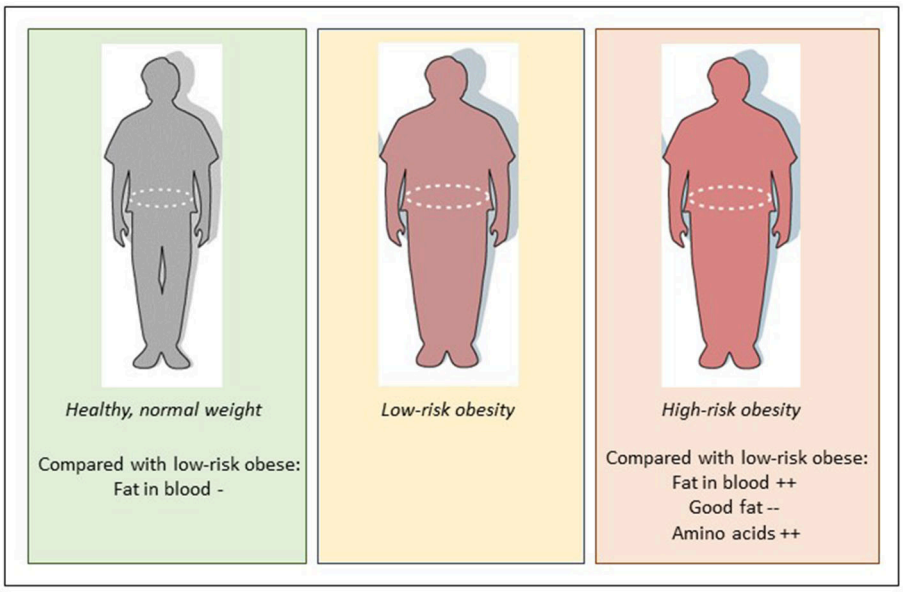

Figure 2

The low-risk obesity profile could possibly be explained by a healthier lifestyle. Although our study did not completely rule out a role of diet, we found no differences in dietary intake of total energy, fat, protein, carbohydrates, or alcohol between people with low-risk obesity and high-risk obesity. In this study we did not measure the participants' regular physical activity level. Physical activity is beneficial for metabolic regulation and might explain some of the differences between the two obesity groups. There may also be genetic variation between the groups explaining the differences. Although we do not yet understand why some people with obesity do not have the same risk of developing metabolic diseases, it is possible that these individuals will have metabolic diseases at a later timepoint. This means that obesity related metabolic diseases may be delayed or even prevented if we know the biomarkers that reflect the risk at an earlier timepoint.

CONCLUSION

People with obesity are diverse—some develop high-risk obesity, while others are more fortunate. Our study found that low-risk obesity is characterized not only by levels of blood glucose and fats in the normal range, but also by other metabolic markers, such as lower circulating levels of amino acids and a broad range of fats. This might mean that some biomarkers may be more predictive of metabolic disease risk. These findings may help to provide a deeper understanding of obesity and its complications, which may eventually improve prevention and treatment of obesity and health.

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ORIGINAL SOURCE ARTICLE

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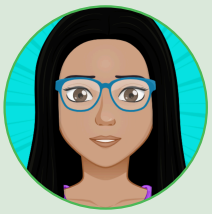
The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

HRISHIKA, AGE: 13
I am Hrishika and I love animals. I like reading realistic fiction and I want to become a doctor when I grow up.



PRIYANKA, AGE: 13

My name is Priyanka and I enjoy reading, drawing, and imagining creative stories about fantasy and magic. My favorite animals are dragons, snakes, and other reptiles. When I grow up I want to become a children's book author and illustrator.

AUTHORS

VIBEKE H. TELLE-HANSEN

I am an associate professor in Nutrition at Oslo Metropolitan University, Norway. My main research interest is to understand how diet and gut microbiota affect metabolic regulation. I am also trying to understand why diet and gut microbiota affect metabolic regulation differently in different groups of individuals. *vtelle@oslomet.no

JACOB J. CHRISTENSEN

Hi! I am Jacob, and I am a clinical dietitian and nutrition researcher who is passionate about how our genes and lifestyle affects the risk of having cardiovascular disease. I especially care about dietary fatty acids and how they affect our health. I also love the programming language R!

GULLA AA. FORMO

I am a clinical dietitian and work as academic director at the Obesity clinic at Aleris hospital in Oslo. I am particularly interested in metabolic health. In my daily work I try to help people and patients to avoid lifestyle diseases due to their obesity through nutrition and lifestyle counseling.

KIRSTEN B. HOLVEN

I am a professor in clinical nutrition at the University of Oslo, Norway. I am trying to understand why some people get heart disease much earlier than other people and how we prevent this. I am especially interested in how we can impact cholesterol levels in blood and if it is important to measure this already as a child.

STINE M. ULVEN

I am a Professor in Nutrition at University of Oslo, Norway. I am particularly interested in understanding why different types of fat have different impact on human health. The goal of my research is to develop dietary guidelines that can be tailor made for specific subgroups of people to prevent lifestyle diseases.

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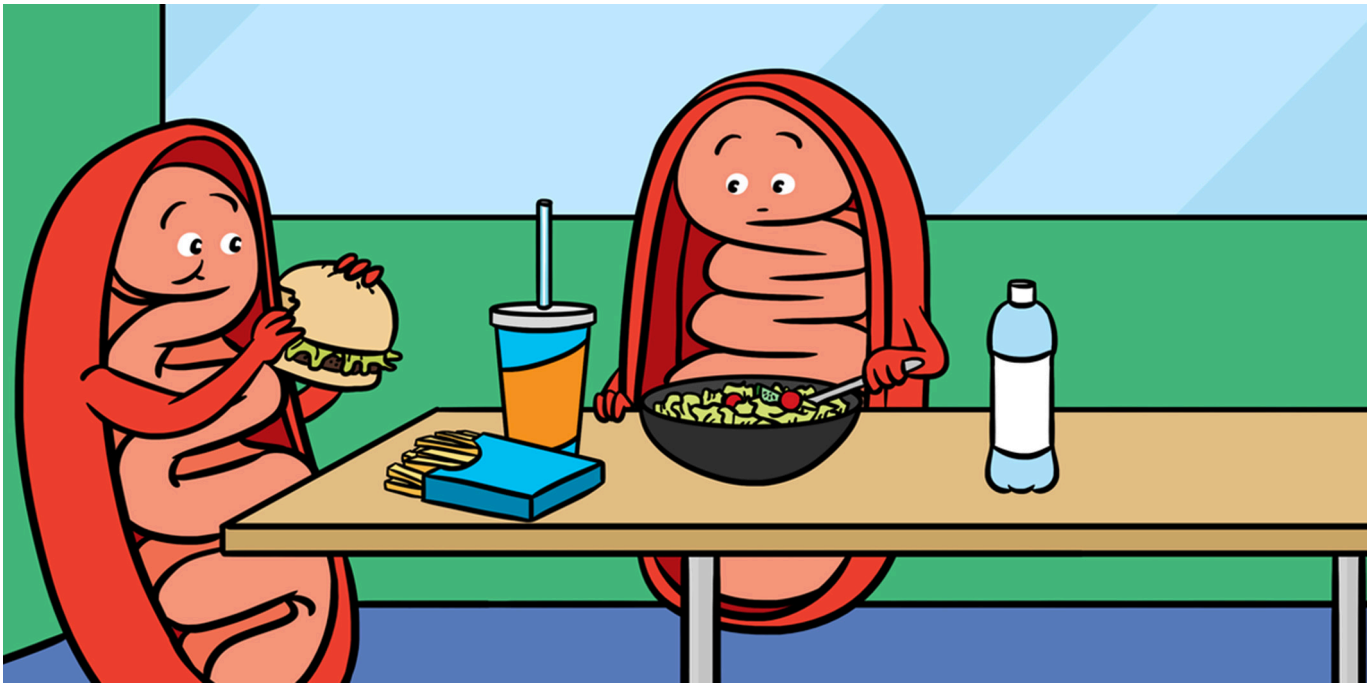

FEED YOUR MITOCHONDRIA AND SHAPE YOUR BODY!

Laura Bordoni* *and Rosita Gabbianelli*

Unit of Molecular Biology and Nutrigenomics, School of Pharmacy, University of Camerino, Camerino, Italy

YOUNG REVIEWERS:


ANASTASIA
AGE: 13


KAÏKE
AGE: 11


KENZO
AGE: 9

If your body were a train, what would give it the power to move? The food you eat, which is burned by the train's engine. Do you know how many engines your body has? Thousands of millions! They are called mitochondria. Mitochondria are tiny structures contained within the cells of your body that burn food, providing energy. The power of each mitochondrion is due to its own gearwheel: the circular mitochondrial DNA. There are many gears in each mitochondrion. Together, they regulate the mitochondrion's ability to produce energy. Obesity modifies both the abundance and the function of the mitochondrial DNA, altering the ability of the body to efficiently produce energy, with some differences between males and females. Eating healthy foods not only makes you slim, but also boosts your mitochondria and makes you powerful!

BODY COMPOSITION: NOT JUST A MATTER OF WEIGHT!

Do you know what makes up your body? The human body can be viewed as a combination of several "packages"—muscle, fat, bones, fluids, organs, ligaments, and tendons. Body weight is a combination of all of these "packages." While everyone's body contains these packages, each body is different in regard to the size of each package (especially fat and muscles). Two people could look similar on the outside and even weigh the same, but be very different on the inside! Determining **body composition** is extremely important: your health is not defined by your body weight, but by your body composition. But how can we see a person's body composition from the outside?

One of the easiest ways to measure body composition includes a combination of body weight, height, and waist circumference. The ratio between weight and height is called body mass index (BMI), and it is commonly used to study obesity in human populations. There are also scientific technologies that can be used to study body composition. Bioimpedance analysis (BIA) measures the ability of the body to resist a weak, painless flow of electric current. Since electric current cannot pass through fat, BIA can estimate the amount of fat and muscles in a person's body. But what if we want to know about how well the body's cells are functioning? There are also methods to collect information about how well the body is working. They rely on sampling body cells or fluids (such as blood or a cheek cells) and measuring some **biomarkers**, which are molecular signals of the body's health or disease status.

MITOCHONDRIA: TURNING FOOD INTO ENERGY

Mitochondria are the powerhouses of the cell. They break down nutrients and, through a sort of "assembly-line," produce energy in the form of substance called **adenosine triphosphate (ATP)**. ATP can then be used by the cell whenever energy is required. This process is also called **cellular respiration**. Mitochondria are small structures **(organelles)** that float freely throughout the cell. Some cells have only a few mitochondria while others have several thousand. If a cell needs more energy to survive, more mitochondria can be created.

Mitochondria are unique organelles because they contain their own DNA (The only other organelle that contains DNA is the nucleus, the commander-in-chief of the cell). The mitochondrial DNA is double stranded (like nuclear DNA), but it is circular, and is present in multiple copies. Mitochondrial DNA can be thought of as a sort of gearwheel that regulates both the number and functions of mitochondria.

BODY COMPOSITION

The content of the body—not only the weight, but also the relative abundance of each body component (fat and muscles in particular).

BIOMARKER

Any measurable parameter or molecule that can give us some hints about the health status of the subject, or could be used to predict the risk of a disease.

MITOCHONDRIA

Small organelles that produce energy (in the form of ATP) by burning food.

ADENOSINE TRIPHOSPHATE (ATP)

A small molecule used by the cell as a type of energy storage. ATP is used for most cellular functions that require energy.

CELLULAR RESPIRATION

A biochemical process, occurring in mitochondria, used by the cell to produce ATP from food.

ORGANELLES

Is a subcellular structure that has one or more specific jobs to perform in the cell.

EPIGENETIC MECHANISMS

A series of biochemical modifications that regulate which proteins are produced from a certain DNA molecule, without modifying its sequence.

DNA METHYLATION

A chemical modification of the DNA that regulates how DNA should be read and, consequentially, whether proteins can be made from it.

Specifically, the higher the number of mitochondrial DNA copies, the higher the mitochondrial abundance and functionality.

Epigenetic mechanisms are one way to regulate the function of DNA, meaning whether the DNA can be used to make proteins with various jobs within the cell. Epigenetic mechanisms modify the 3D structure of the DNA molecule, making it either more "open" (functional/active) or more "closed" (inactive) (Figure 1). One of the most important epigenetic mechanisms is called **DNA methylation**, which is the addition of a chemical structure called a methyl group (CH_3) to the DNA. We can imagine methyl groups as "flags" that can be added to or removed from specific DNA sequences to regulate them [1, 2].

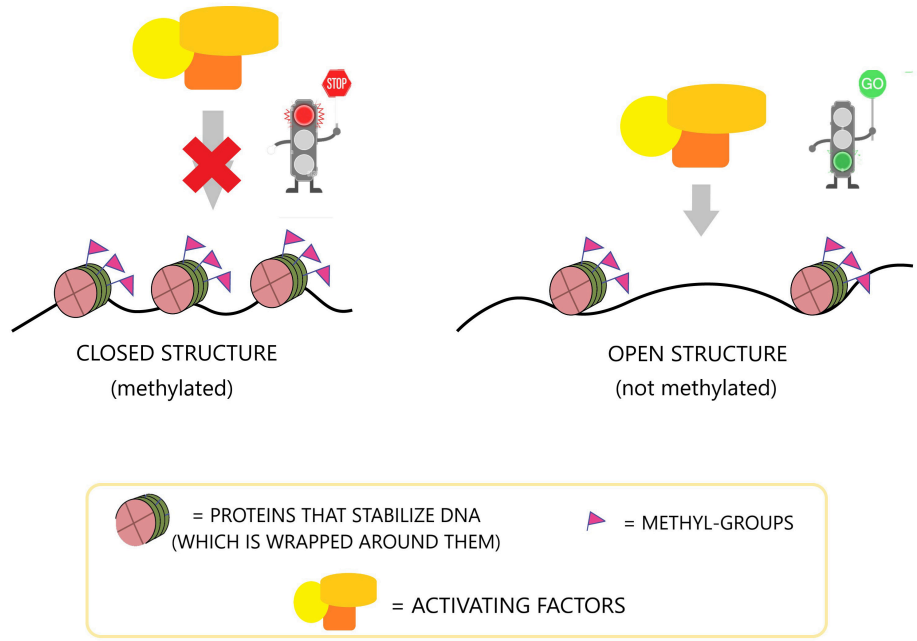

Figure 1

Epigenetic mechanisms, such as DNA methylation (flags), affect the activity of DNA molecules by regulating whether the DNA is "open" (functional/active) or "closed" (inactive). "Open" sections of DNA are accessible to activating factors that lead to protein production. Whether methylation works the same way in mitochondrial DNA is currently under investigation.

It has recently been suggested that, like nuclear DNA, the function of mitochondrial DNA might also be regulated methylation (Figure 2), especially in a regulatory area called the D-loop. Our cells obtain methyl groups from the foods we eat. Food provides us with both methyl groups and the B vitamins that help methyl groups move around inside cells. Since methyl groups regulate the functions of DNA, they are very important! Incorrect DNA "flagging" is associated with disease, and improper methylation of mitochondrial DNA might cause poor mitochondrial function!

OVERWEIGHT GIRLS HAVE REDUCED MITOCHONDRIAL POWER

A group of adolescents from central Italy was recruited to study the association between body composition and mitochondrial DNA status.

Figure 2

Mitochondria burn food to produce energy, so they are the powerhouses of the cell. The circular molecules of mitochondrial DNA (mtDNA) contained in the mitochondrion help to regulate its functions.

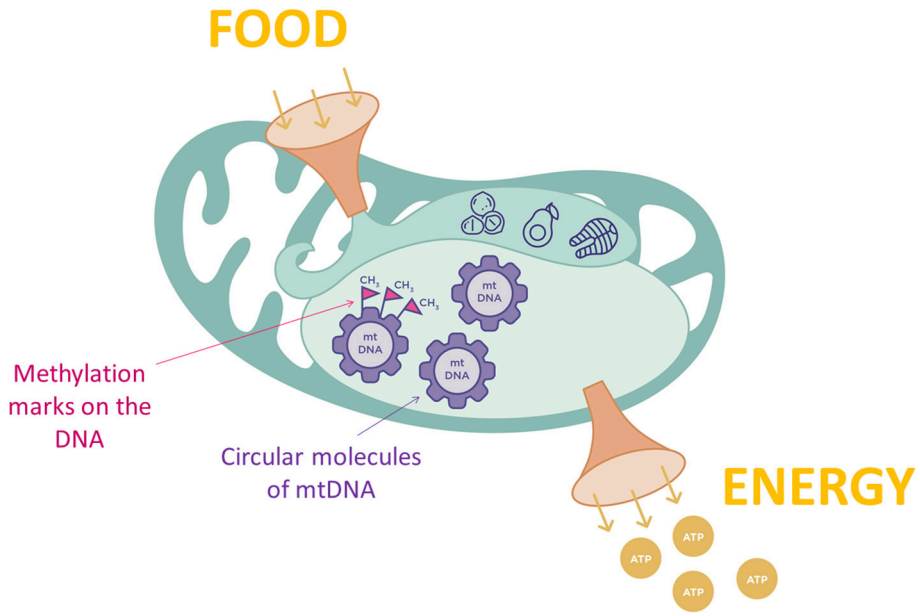

Figure 2

Mitochondrial DNA was extracted from cheek swabs (collecting cells from the inner part of the cheek, inside the mouth) and the abundance of mitochondrial DNA copies and D-loop methylation were measured. Results showed that there were fewer copies of mitochondrial DNA in overweight subjects (Figure 3A).

Moreover, overweight subjects showed higher levels of methyl groups in the D-loops of their mitochondrial DNA (Figure 3B). This suggests that problems with mitochondrial function might occur in individuals with an unfavorable body composition, even when they are young. In boys, we saw only small differences in mitochondrial biomarkers so, to know for sure whether obesity is correlated with mitochondrial DNA methylation in boys, more samples must be studied.

MITOCHONDRIAL EPIGENETICS AS A BIOMARKER?

A reduced number of mitochondrial DNA copies and increased methylation levels might be associated with reduced functioning of mitochondria. It looks like the condition of being overweight might favor these mitochondrial changes. The exact mechanisms through which mitochondria DNA methylation and copy number affect the functions of mitochondria are still being studied. Despite many missing details, it appears that the state of the mitochondria may be an interesting biomarker of cellular health. Mitochondrial biomarkers seem to vary as a consequence of exposures to pollution or tobacco smoke [3] and in diseases like cardiovascular disease [4]. Since diet is also an environmental exposure, mitochondrial biomarkers might represent a sort of "alarm signal" that could be easily measured

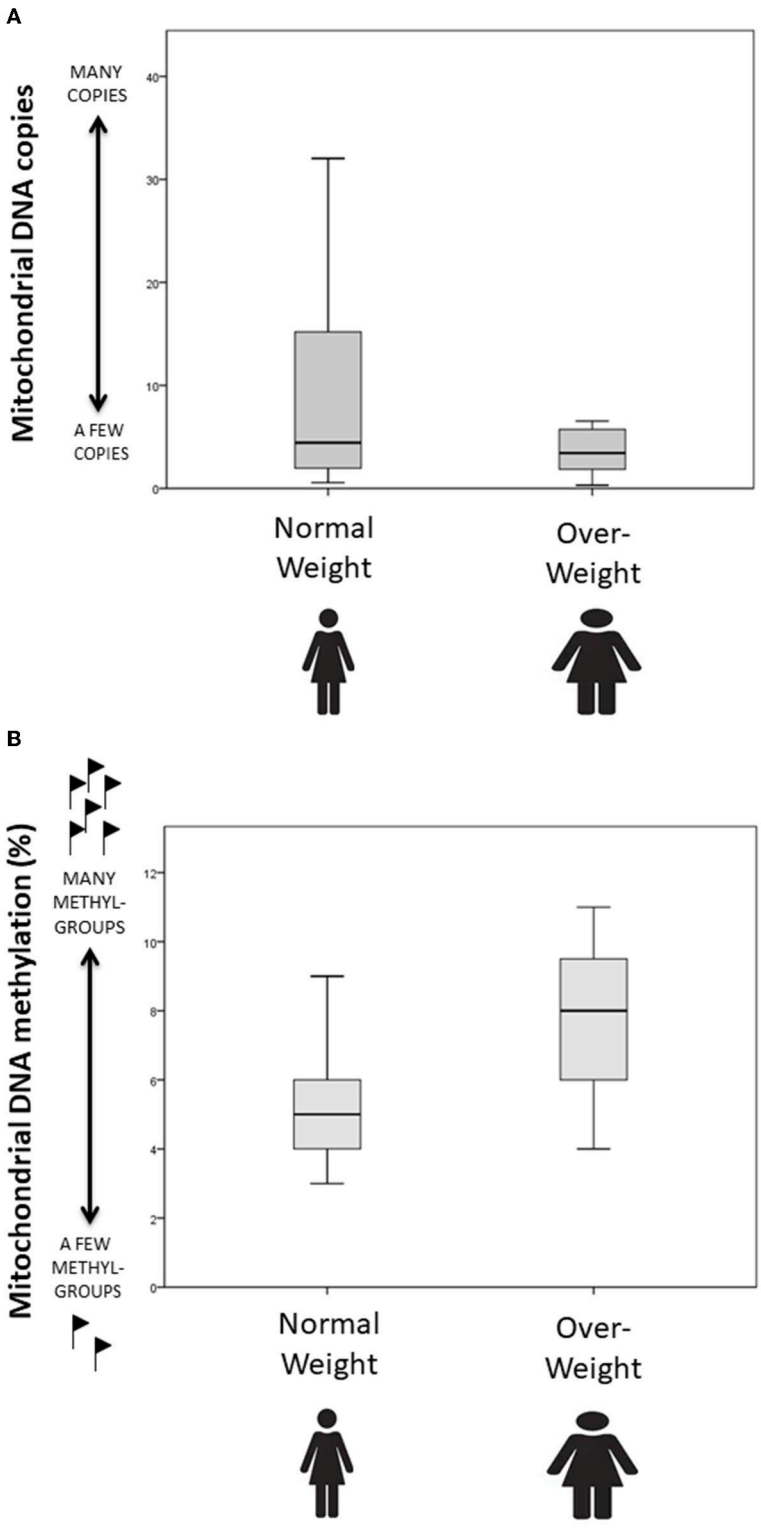

Figure 3

(A) The number of copies of mitochondrial DNA is reduced in obese and overweight girls compared with lean girls. **(B)** Mitochondrial DNA methylation is higher in obese and overweight girls compared with lean girls[1].

[1] The box and the "whiskers" represent all the measured values. The box includes half of the measured values. The "whiskers" include the remaining half of the measurements (25% for each whisker). If most of the measurements are close the mean (the central line), the box will be small; if there is a lot of variability in the values, the box will be larger.

at an early stage, before unbalanced diets and unhealthy lifestyles cause serious problems [5]. Hopefully, future studies will confirm that measures of mitochondrial DNA copy number and methylation status can be used as a biomarker of health.

LOOKING TO THE FUTURE

Nutrition and physical activity, along with genetics and age, determine how much fat and muscle each person has inside their body. If we have unhealthy eating habits and are not active, our bodies store extra fat that they do not need. Unhealthy body composition and poor diet have consequences not only on body shape but, more importantly, on body functions. Specifically, an unhealthy body composition might impair the activity of mitochondria and their ability to produce energy efficiently, while eating healthy foods keeps the body lean and powerful. This is not only because healthy foods are good fuel for our cells, but also because healthy foods keep the engine of our cellular powerhouses—the mitochondrial DNA—properly functioning. This is why balanced nutrition, together with moderate physical activity, makes us feel healthy and energetic.

This study suggests that poorly regulated epigenetic mechanisms, specifically DNA methylation, might happen in obese girls, highlighting a way that mitochondrial functions might be regulated. However, always remember that scientific evidence can be confirmed only after many repetitions! Further experiments using more samples are necessary to confirm these findings. Replication of experiments might also help to clarify the inconclusive findings that we saw in boys in our study. We hope that the new findings emerging from this work will encourage the scientific community to keep investigating mitochondrial DNA methylation, because such studies might provide new insights on the effects of diet on human health.

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ORIGINAL SOURCE ARTICLE

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YOUNG REVIEWERS

ANASTASIA, AGE: 13
I am Anastasia, a year 9 student captivated by science! I am very passionate about learning and discovering new opportunities. My dream is to study medicine, as I am very interested in how our body works and how it can be affected. Outside of my studies, I love painting, drawing, and crafting, as well as many other extracurricular clubs. But most of all, I love cooking deserts (I have a sweet tooth)!

KAÏKE, AGE: 11
My name is Kaïke. I love football, gaming, and eating. I am from Brazil, France, Egypt, America, Lebanon, Italy, and Syria. I have many friends and I love seeing them. I also love anime. My favorite Animés are Naruto, Dragon ball Z, and Demon slayer. I am a very good baker and I cook lot of cakes and cookies. My favorite football player is Cristiano Ronaldo and my favorite team is Manchester United and Real Madrid.

KENZO, AGE: 9

Hi, I am 9 years old, always exited and super friendly. I have a lot of friends and make new friends easily. I like listening to songs and playing video games. I also really like fighting and self defense. My favorite hobby is parkour. At school, I enjoy sports, arts, math, and the breaks. I often express my thoughts and talk while the teacher explains so time goes faster ☺. I love reading comics.

AUTHORS

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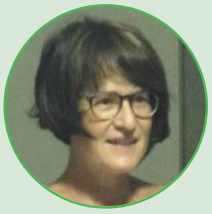
Laura Bordoni is Assistant Professor at the School of Pharmacy, University of Camerino, Italy. She obtained her Ph.D. in Life and Health Sciences—Molecular Biology and Cellular Biotechnology in 2017. She is professor of Food Science, Nutrition, and Molecular Biology at University of Camerino and visiting professor of Molecular Biology at Jilin Agriculture University, Changchun (China). Her research is focused on nutrigenomics, investigating the interactions between diet and the human genome to understand how nutrition can promote healthy aging. In particular, she is currently investigating how different diets (healthy vs. western) and dietary metabolites (such as trimethylamine and its derivative trimethylamine-N-oxide) can impact DNA methylation in humans. She is co(author) of 29 peer-reviewed publication, three book chapters and several communications at national and international meetings. She is guest-editor for several journals in the field of nutrition, biochemistry, and molecular biology. Website: https://docenti.unicam.it/pdett.aspx?ids=N&tv=d&UteId=1128&ru=RD *laura.bordoni@unicam.it



ROSITA GABBIANELLI

Rosita Gabbianelli, is Full Professor of Biochemistry at University of Camerino, Italy. She obtained her Ph.D. in Biology in 1997. Her research field includes studies on the interplay between the exposome and health, and the nutrigenomic strategies to counterbalance molecular damage. She is visiting professor at Jilin Agriculture University, Changchun (China) and (co)author of more than 130 peer-reviewed publications, four chapters of books and 138 communications at international meetings and 45 seminars to general audience. She has supervised more than 84 bachelor/master degree/Ph.D. students. She is an editorial board member of several journals on health and member of NUGO, SIB, CA18211, CA20104, and CA19115. Board of Directors of the International Society of Nutrigenetics and Nutrigenomics and Chair of the Scientific and Organizing Committee of the European Summer School on Nutrigenomics. Website: https://docenti.unicam.it/pdett.aspx?UteId=448&tv=d&ru=PA

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HOW DOES LIFESTYLE AFFECT COLORECTAL CANCER RISK?

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YOUNG REVIEWER:

COOPER

AGE: 14

Lifestyle—what we eat, how much exercise we do, and how much we weigh, can change our chances of getting diseases like cancer in the large intestine (colorectal cancer). The World Cancer Research Fund has come up with eight lifestyle recommendations to lower our chances of getting cancer. For example, we are recommended to eat at least five servings of fruits and vegetables every day. It is also important that we understand how our lifestyles, and following these recommendations, affects our chances of getting cancer. How does a healthier diet, doing more exercise, and maintaining a healthy weight affect the biological processes that lead to cancer? In our study, we wanted to find out how sticking to these Cancer Prevention Recommendations could keep us protected from cancers in the large intestine.

HEALTHIER LIFESTYLES REDUCE CANCER RISK

The foods we eat, how much we exercise, and how much we weigh are all part of our lifestyle. The healthiness of our lifestyle affects how likely we are to develop diseases such as heart disease and some cancers. Cancer is a disease that affects the body's cells and makes them grow out of control. A person's chances of getting cancer depend on their genes and their age, but cancer risk can also be affected by lifestyle. Did you know that about 40% of cancers could be prevented by having a healthier lifestyle? Scientists have found that eating particular foods and nutrients can change the chances of getting some cancers. But we do not usually eat just single foods or nutrients, do we? We eat meals and lots of different foods each day. This means that it is important to look at a person's entire lifestyle—what they eat and do overall. We can measure how healthy a person's lifestyle is by seeing how closely what they do matches with lifestyle recommendations.

The World Cancer Research Fund (WCRF) has written guidelines called Cancer Prevention Recommendations to help people lead healthier lifestyles and reduce their chances of getting cancer and other diseases[1]. These guidelines include eight separate tips (Figure 1) related to food, exercise, and body weight. For example, we are asked to do lots of exercise and eat plenty of fruits and vegetables. Some studies have found that people who stick to the Cancer Prevention Recommendations have a lower chance of getting cancers [1] such as **colorectal cancer** (in the large intestine). The next steps are for scientists to investigate why and how this happens. What are the biological processes in the large intestine that are affected by following these recommendations? How could these processes change our chances of getting colorectal cancer?

Figure 1

CANCERS GROWING IN THE LARGE INTESTINE

The large intestine is one organ that might especially benefit from a healthy diet. The large intestine is the last part of the digestive system and grows to be about 1.5 m long. Its main job is to absorb water and nutrients, and to pass undigested food out of the body. The inside

[1] World Cancer Research Fund International. Diet, Activity and Cancer: Cancer Prevention Recommendations. Available at: www.wcrf.org/diet-and-cancer/cancer-prevention-recommendations/.

COLORECTAL CANCER

A disease that results from cells in the large intestine growing out of control.

Figure 1

The WCRF Cancer Prevention Recommendations include eight lifestyle tips to help to reduce the chances of getting cancer. For example, it is recommended that we eat no more than 500 g of red meat per week, and very little processed meat. In our study, we did not collect information on sugary drink intake, but we added the non-smoking recommendation. People scored 0 or 1 for each recommendation (or 0 or 0.5 for the fruits, vegetables, and dietary fiber recommendations) and we added these scores up to determine the total score out of eight points.

CRYPTS

The dips that line the large intestine.

of the large intestine is covered in small dips called **crypts** (Figure 2), which contain the cells that absorb water and nutrients. Scientists can tell how healthy the large intestine is by checking how many cells are growing inside these crypts. If the cells grow too quickly or there are too many, they can turn into colorectal cancer. Scientists have done lots of research to show links between lifestyle and the chances of getting colorectal cancer. For example, eating too much red and processed meat, like beef steaks and pork sausages, can increase a person's chances of getting colorectal cancer.

Figure 2

The inside of the large intestine is lined with dips called colorectal crypts. These crypts are lined with cells from the bottom of the crypt (base) to the top of the crypt (mouth). In healthy crypts, most of the growing cells are found toward the base. We used a special dye to stain growing cells purple and examined them using a microscope. If more purple cells are seen toward the mouths of the crypts, it can indicate a higher chance of colorectal cancer.

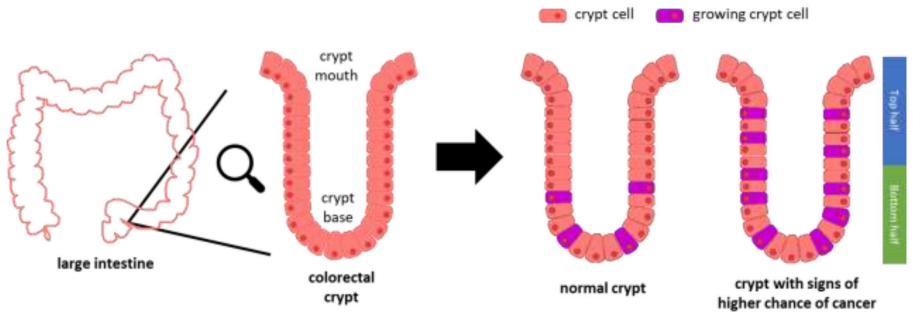

Figure 2

STUDYING LIFESTYLE CHANGES AND COLORECTAL CANCER

In our study, we investigated whether people who followed the Cancer Prevention Recommendations have healthier large intestines, meaning lower chances of colorectal cancer. Seventy-five healthy adults joined and completed the study. We weighed each person and took their body measurements. They filled out questionnaires about which foods they ate and how much exercise they did. We used this information to calculate a total score for how well our study participants followed the Cancer Prevention Recommendations.

We created a scoring system that included seven of the recommendations (see Figure 1), along with an extra recommendation about smoking, as smoking also increases cancer risk. For each recommendation, we gave 1 point to each person who followed it, and 0 points to people who did not. For example, people who ate more than 500 g (about three portions) of red meat every week scored 0 points for that recommendation. The recommendation on plant foods was divided into two: eat at least five servings of fruits and vegetables per day; and eat at least 25 g of dietary fiber per day. For these, we gave 0.5 points to those who followed the recommendations and 0 points to those who did not. Therefore, the total score for the recommendations dealing with plant foods was still a maximum of 1 point. We then added up the scores for each recommendation and gave each participant a final mark out of the possible total of 8 points.

BIOPSY

A tiny sample of tissue collected from the body, including the large intestine.

COLONOSCOPE

A long, flexible tube with a tiny light and camera used to examine inside the large intestine.

RIBONUCLEIC ACID (RNA)

Molecules made from the information in DNA, which are used to make the proteins that build cells.

POLYMERASE CHAIN REACTION

A lab technique that lets scientists look at a specific sequence of DNA or RNA, for example to measure the activity of a gene.

C-MYC

A gene belonging to the WNT family that regulates many processes in the body including controlling how much cells grow.

Figure 3

(A) Higher total scores were related to lower levels of genes that control how much cells grow, such as a gene called *c-MYC*. Each blue dot represents the *c-MYC* gene level for 40 of the participants in our study. **(B)** Using a microscope, we found a greater percentage of cells growing in the top halfs of crypts in people who scored 0 for the red- and processed-meat recommendation (70 participants). **(C)** Lower levels of *WNT11* were found in the large intestines of people who followed the recommendations to eat plenty of dietary fiber and to do lots of physical activity (50 participants).

In the hospital, we collected tiny pinches of tissue called **biopsies** from the study participants' large intestines, using a tube-like camera called a **colonoscope**. In the laboratory, we used a special dye to stain the cells in the crypts, to determine whether they were growing. Looking through a microscope, we zoomed in on the crypts and counted the growing cells, as well as their positions in the crypts. We calculated how many growing cells were in the bottom half of the crypt (the base), and how many were toward the top of the crypt (the mouth). This is important because, when the large intestine is healthy, most of the growing cells are in the bottom (base) of the crypts. When more cells start growing toward the top (mouth) of the crypt, it could indicate an increased chance of colorectal cancer.

We also extracted **RNA** from the cells in the biopsies. RNA is a molecule that carries information from our genes (DNA) and is used to build parts of our cells. We measured whether genes were turned on or off using a laboratory technique called **polymerase chain reaction**. We measured the genes that help to control cell growth in the large intestine, which are known to be involved in colorectal cancer.

WHAT DID WE FIND?

Most of the people in our study scored between 2 and 4 points out of a maximum of 8. The great news is that nobody scored 0 points! People who had higher scores, and therefore led healthier lifestyles, had lower levels of the genes that can play a role in colorectal cancer. We measured the activity (how much they were turned "on" or "off") of a family of genes called the WNT pathway, that regulate important processes in our body such as how much cells grow. One of these genes is called **c-MYC**. Levels of *c-MYC* got lower as total scores got higher (Figure 3A), and participants who had more than 3 points had almost half the amount of *c-MYC* compared with those who scored <3 points.

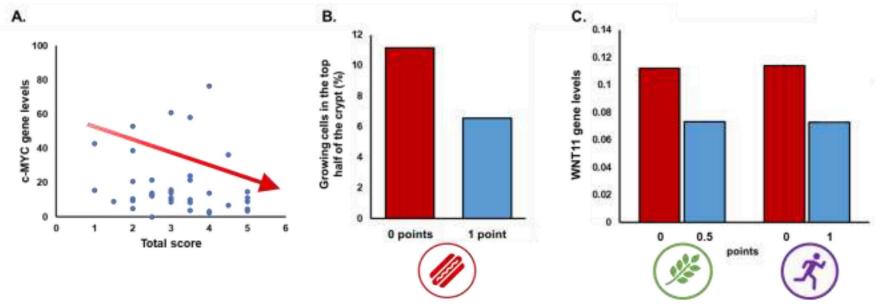

Figure 3

We also looked at scores for each of the individual Cancer Prevention Recommendations. We saw interesting results when we compared study participants who did and did not follow the recommendation

to eat <500 g of red meat per week. We counted 70% more growing cells in the top halves of the crypts in participants who ate more than 500 g of red meat per week than we counted in people who followed this recommendation (Figure 3B). This finding supports the results of many experiments in both animals and humans: eating lots of red meat (such as beef burgers) and processed meats (such as ham or bacon), increases the chance of getting colorectal cancer. This is because some of the molecules in red meat can damage cells. Our results show that eating too much red and processed meat could increase the chance of getting colorectal cancer by changing how much, and in which part of the crypts, cells are growing.

You may know that eating lots of dietary fiber, found in foods like wholegrain cereals and vegetables, is good for the gut. When dietary fiber reaches the large intestine, it feeds the bacteria that live there. These bacteria have healthy effects in our bodies [2] and they can also help stop the growth of cancers. We found one third lower activity of the gene called **WNT11** in people who followed this fiber recommendation compared with those who scored 0. *WNT11*, like *c-MYC,* is another member of the WNT pathway family that can help to control cell growth. People who did more exercise also had lower levels of *WNT11* genes, by about a third (Figure 3C). Overall, scoring full marks for some of the recommendations is linked to better control of the WNT pathway and so a lower chance of developing colorectal cancer.

WNT11

A gene belonging to the WNT family that regulates many processes in the body including controlling how much cells grow.

TAKE-HOME MESSAGE

What a person eats, how much exercise they do, and how healthy their body weight is are all part of that person's lifestyle. A healthier lifestyle lowers the risk of diseases such as colorectal cancer. We wondered how lifestyle could affect the biological processes that can cause cancers in the large intestine. Our experiments showed that one of the ways lifestyle does this is by affecting how quickly the cells inside the large intestine grow and where those growing cells are located in the crypts. What we eat and how much physical activity we do can influence these cells by turning genes that control cell growth on or off.

Encouraging people to follow the WCRF Cancer Prevention Recommendations can lead to healthier large intestines and can lower their chances of getting colorectal cancer. How many of the recommendations are you following at the moment? Do you think that you could improve your score? For example, could you cut down on the number of beef burgers and sausages that you eat, and eat more fruits and vegetables?

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YOUNG REVIEWER

COOPER, AGE: 14

Hi my name is Cooper. I love to play basketball and hang out with my friends. I am in grade 9 and my favorite subject is math. I also enjoy drawing and cooking.

AUTHORS

FIONA C. MALCOMSON

Fiona C. Malcomson is a research scientist at Newcastle University in the UK. Her research focuses on how we can reduce the risk of developing certain cancers through changes to our lifestyles, such as our diets and levels of physical activity. In particular, Fiona C. Malcomson is interested in the mechanisms for how what we eat, for example how much dietary fiber we eat, affects the risk of developing cancer in the large intestine. *fiona.malcomson@newcastle.ac.uk

NAOMI D. WILLIS

Naomi D. Willis spent 6 years working as a research scientist at Newcastle University in the UK, where she followed her interest in finding ways to prevent colorectal cancer. Her work initially looked at changes in gut health linked to what we eat. She later ran a study to identify specific chemicals in urine that could be used to measure whether someone has a healthy diet. She now helps other researchers to develop their scientific inventions, to make them suitable for real-world use to improve people's lives.

JOHN C. MATHERS

John C. Mathers is a professor of human nutrition at Newcastle University in the UK. In addition to teaching students about nutrition and health, he carries out research on nutrition and aging and on the risk of age-related diseases. He was one of the founding members of NuGO—the European Nutrigenomics Organization—that has pioneered the use of modern molecular methods for studying how what we eat affects health. John is using those methods to investigate links between eating habits and common diseases, including colorectal cancer.

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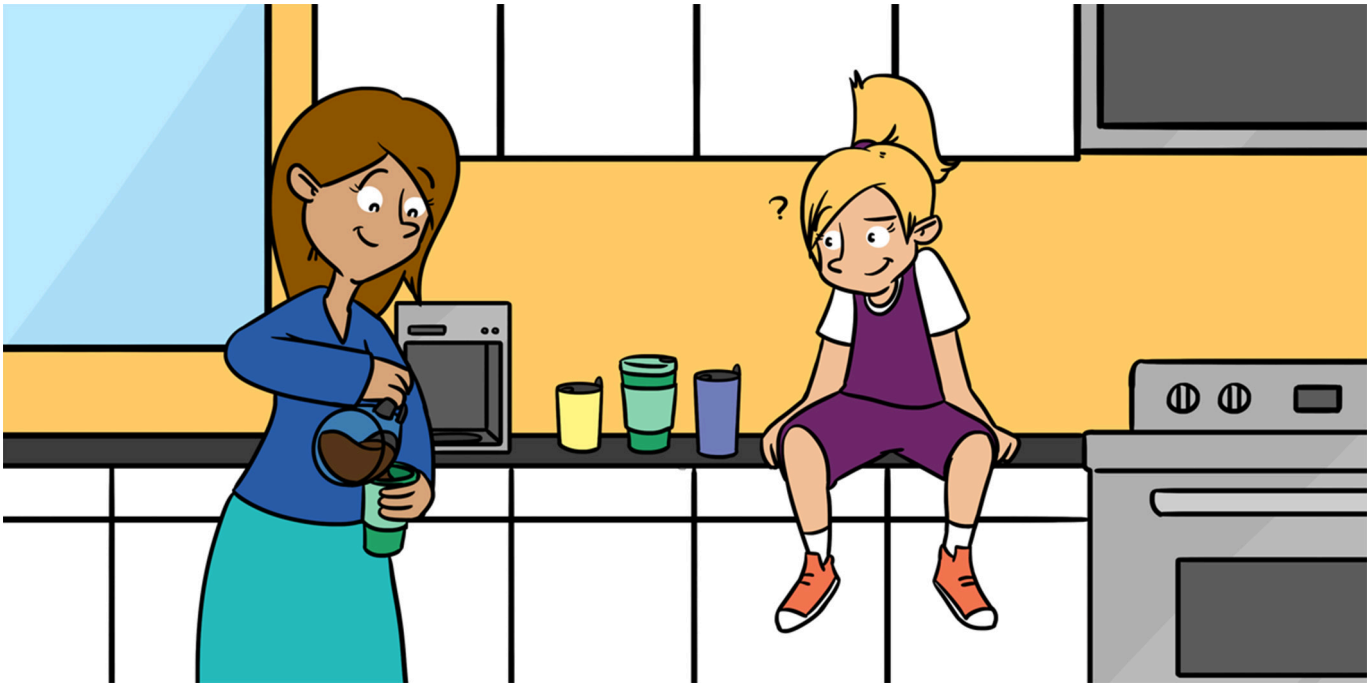

COFFEE: IS IT A FRIEND OR A FOE?

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AGE: 11

Coffee is not only one of the most consumed drinks in the world, it is also one of the most addicting. Coffee is complex—it is made up of many substances. One of coffee's components is of special interest to the scientific community: caffeine. Caffeine has several important effects on the body, and these effects differ whether caffeine is taken once in a while or regularly. Also, it has been shown in both animal studies and in humans that, if caffeine is consumed regularly, it might affect several diseases, including diseases of the heart and metabolism.

COFFEE AND ITS COMPOUNDS

Everyone knows how to prepare coffee: pour boiling water onto roasted, ground up coffee beans and brew them. Although it has a bitter taste, coffee is one of the most consumed drinks in the world and an adult favorite. If it is bitter, why do people love it so much? The answer is simple: coffee is a natural stimulant, which means it gives people an energy boost to get them through the day.

Coffee contains a variety of substances such as fats, proteins, and sugars. This makes it a rich substance with many different effects on our bodies. One of coffee's best-known ingredients is caffeine, which is responsible for the energy boost we get from drinking this beverage [1]. But caffeine is not present in just coffee—it is contained in other things we eat and drink as well.

HOW AND WHERE DO WE CONSUME CAFFEINE?

Chocolate, sodas, and green and black tea are examples of foods or drinks that contain caffeine (Figure 1). What about the many different types of coffees—are they all the same? Coffee that is brewed in a coffee pot like you might have in your home has about 57 mg of caffeine per 1.8 g of grounded beans. Espresso, made by specific machines and often sold in coffee shops, has between 40 and 75 mg of caffeine in 30 ml of coffee. Decaf coffee has the least caffeine, with about 3 mg per 150 ml. To make decaf coffee, the beans undergo treatments to remove the caffeine [2]. Since it has low amounts of caffeine, decaf is often thought to be the best for human health. But, as you will soon learn, this might not be the case.

Figure 1

Amounts of caffeine in various food products. One coffee bean represents 6 mg of caffeine. A cup of coffee has about 90 mg of caffeine, while a cup of tea has about 45 mg. A 44 g piece of milk chocolate has ~10 mg of caffeine. A typical soda contains 35 mg of caffeine.

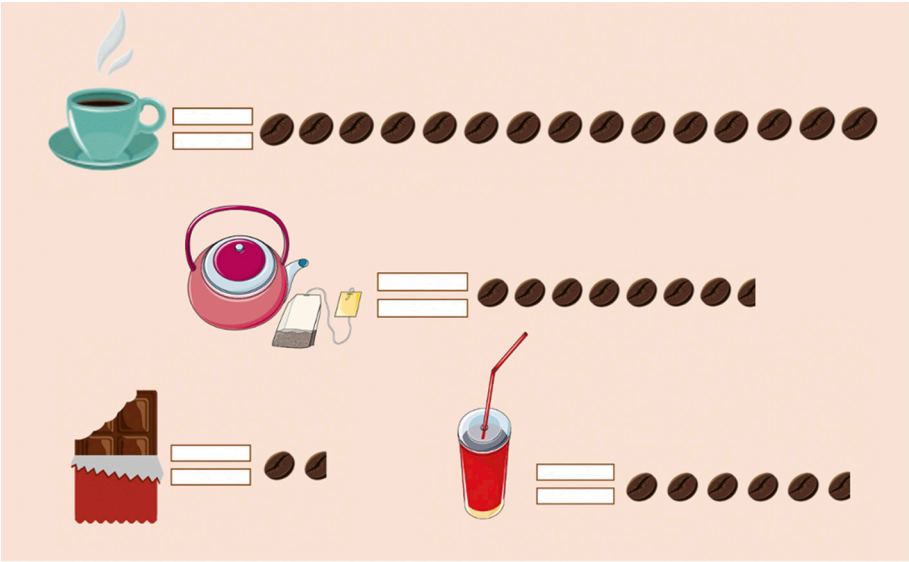

Figure 1

COFFEE IN CARDIOMETABOLIC DISEASES

CARDIOMETABOLIC DISEASES

Diseases that affect the reactions within our cells that use the nutrients from the food to produce energy and make all our organs function.

Have you ever heard of **cardiometabolic diseases**? These are diseases that affect the reactions within our cells that use the nutrients from the food to produce energy and make all our organs functioning. Diabetes, high blood pressure, and obesity are well-known examples of cardiometabolic diseases. Type 2 diabetes results in increased levels of sugar (glucose) in the blood. Normally, a hormone called insulin

keeps blood sugar low because it helps glucose to enter into the body's cells, but in type 2 diabetes, the cells do not respond to insulin, resulting in a state called **insulin resistance**. High blood pressure happens when the force exerted by the blood on the walls of the arteries is high. Obesity is the presence of an excessive amount of fat in the body. These three diseases are the result of changes in the body's **metabolism**, meaning changes in the reactions using nutrients from food. Later in life, these diseases can lead to other negative health effects, like strokes and heart attacks.

INSULIN RESISTANCE

State in which cells from insulin-sensitive tissues do not respond correctly to insulin.

METABOLISM

Reactions using nutrients from food.

For a long time, scientists have debated the effects of coffee in people who have cardiometabolic diseases. At first, coffee was believed to have negative consequences for these diseases, but recent studies show that this might be a myth.

WHAT DOES CAFFEINE DO IN THE BODY?

After ingestion, caffeine is absorbed by the digestive system, circulates in the blood, and ends its journey in the liver. It interacts with the body in many ways and in various tissues (Figure 2). Caffeine acts by inhibiting **adenosine receptors**, which are molecules on the surfaces of cells that bind to a substance called adenosine. What is **adenosine**? It is a molecule involved in cell-to-cell conversations and in the production of energy. Adenosine has several functions, including the regulation of blood sugar levels. Because caffeine is similar to adenosine, it also sticks to the adenosine receptor. This means that fewer adenosine receptors will be available to bind to adenosine. Think of it as a game of musical chairs—the receptor is the only chair and caffeine and adenosine are the players that want the coveted spot. When adenosine loses the "game," the activity of adenosine in the body decreases and the activity of caffeine increases. Caffeine intake activates the **sympathetic nervous system** (SNS), which is the part of the nervous system that controls some of our unconscious actions. One of these actions is the "fight-or-flight" response. By activating the SNS, caffeine increases the body's production of a hormone called **adrenaline**, which sends a message to the body to stay awake and alert and to feel less bored.

ADENOSINE RECEPTORS

Molecules on the surfaces of cells, to which adenosine binds to exert its function.

ADENOSINE

A molecule involved in cell-to-cell conversations and in the production of energy.

SYMPATHETIC NERVOUS SYSTEM

The part of the nervous system that controls some of our unconscious actions.

ADRENALINE

Hormone that sends messages to the body to stay awake and alert and to feel less bored.

The best way to define caffeine is as a double-edged sword. On one side, we have the effects of occasional consumption—consuming caffeine once in a while—and, on the other, the effects of regular consumption—consuming caffeine on a daily basis. When we drink a cup of coffee once in a while, caffeine has a negative impact on the body. The SNS becomes activated, which leads to an increase in insulin resistance. The sugar present in the blood will not be able to enter the cells, which increases blood sugar levels. Due to this fact, for many years scientists and medical doctors believed that caffeine was bad for patients with cardiometabolic diseases [3].

Figure 2

Caffeine operates on multiple systems in the body including (clockwise from top) the heart, muscles, fat, liver, and brain.

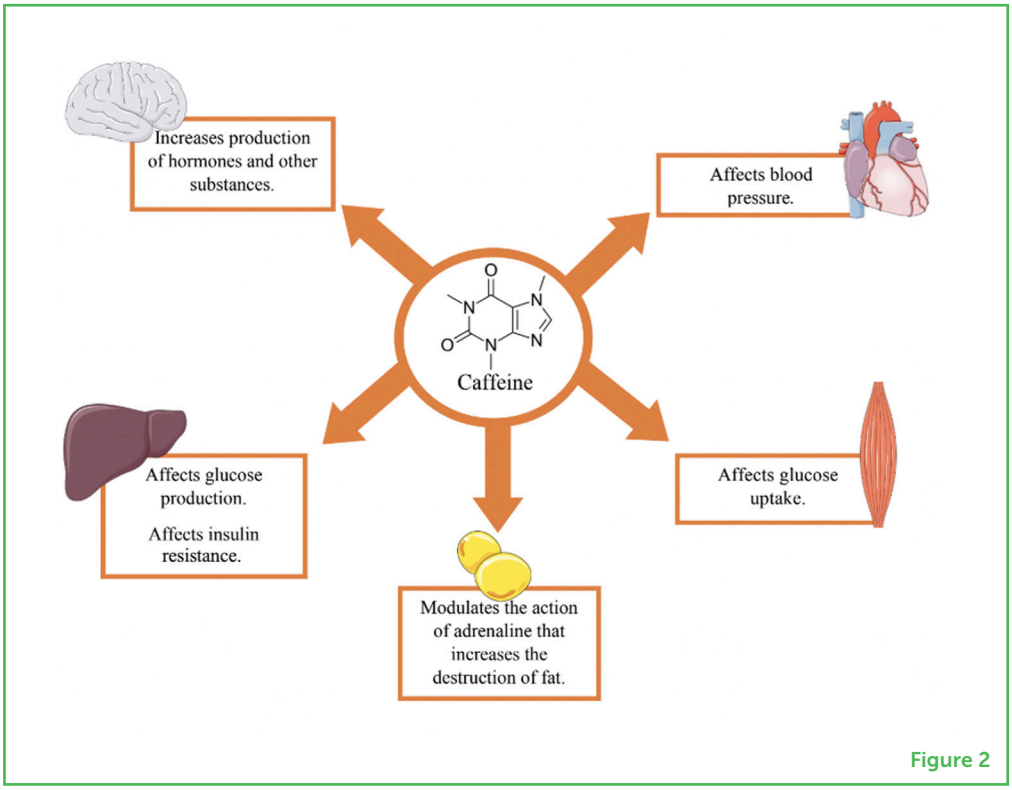

Figure 2

When we talk about regular caffeine consumption, we may see the opposite happening. When there is a regular intake of caffeine, the body gets used to it. Since caffeine and adenosine compete for the same receptors, the number of adenosine receptors in the body increases. In fact, coffee consumption may be beneficial for people with diabetes. Regular coffee consumption can decrease insulin resistance and lower blood sugar levels [2].

People with heart and blood circulation problems are commonly advised to limit caffeine intake. This advice is based on studies showing that caffeine can increase blood pressure. But several studies show the opposite effect, indicating that high coffee consumption, equivalent to around 4–5 coffees per day for at least 2 weeks, can lead to some protection against heart and circulation diseases [4].

Last, obesity is one of the major health problems of this century. Doctors strongly warn patients to limit how much and what kinds of foods they eat. Scientists do not understand why yet, but some studies show that caffeine intake reduces the amount of fat in the body [1].

DOES CAFFEINE BURN FAT?

How does caffeine burn body fat and decrease obesity and other cardiometabolic diseases? There are several theories. One theory says that caffeine increases adrenaline production, which increases

alertness and promotes weight loss. In the body, adrenaline increases the destruction of fat through a process called lipolysis [4]. Another theory involves the role of "good fat," called brown adipose tissue. This good fat helps to eliminate the "bad fat," called white adipose tissue. A study from the University of Nottingham showed that, after drinking coffee, metabolism accelerates due to activation of good fat, the brown fat, and the body releases more energy in the form of heat [5].

CAN CAFFEINE HELP CARDIOMETABOLIC DISEASES?

Studies have also shown that adenosine regulates insulin production and decreases insulin resistance, which helps glucose to enter the cells [3]. One lab studied the effects of caffeine in cardiometabolic diseases in rats. Rats ate a diet with high amounts of fat and sugar, until they developed insulin resistance and high blood pressure. Caffeine treatment reversed the insulin resistance [3].

VASODILATION

The widening of blood vessels.

Long-term caffeine intake can increase **vasodilatation**, which is the widening of blood vessels This means that caffeine might be useful as treatment to lower blood pressure [4, 6]. Vasodilation can also decrease insulin resistance because, when vasodilation increases, more insulin will reach the organs, which promotes the entry of glucose into cells. Also, in a study on old rats, caffeine did not increase the rats' blood pressure. Several studies were also carried out in humans, showing that high caffeine intake may *not* increase the risk of high blood pressure [4]. All of these studies show that long-term caffeine intake will benefit the treatment of cardiometabolic diseases.

CONCLUSION

So, is caffeine a friend or foe when it comes to cardiometabolic diseases? This is still an open question—caffeine can be an ally or an enemy, depending on a variety of factors that should be evaluated for each person, with the help of a doctor. Several studies are currently being done to learn more about what caffeine does to the body and the best way to consume it. Based on the most relevant studies, we can say that regular coffee consumption might have more good effects than bad effects, but exactly how caffeine circulates through the body and how it impacts metabolism are still not completely understood. One thing is for certain: understanding the effects of caffeine is a topic that still needs to be studied in more depth.

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I enjoy playing many sports, especially soccer. I like hanging out with my family/friends. The school subjects that I like the most are math, art, and social studies. I love watching "Full House." My favorite color is teal blue.

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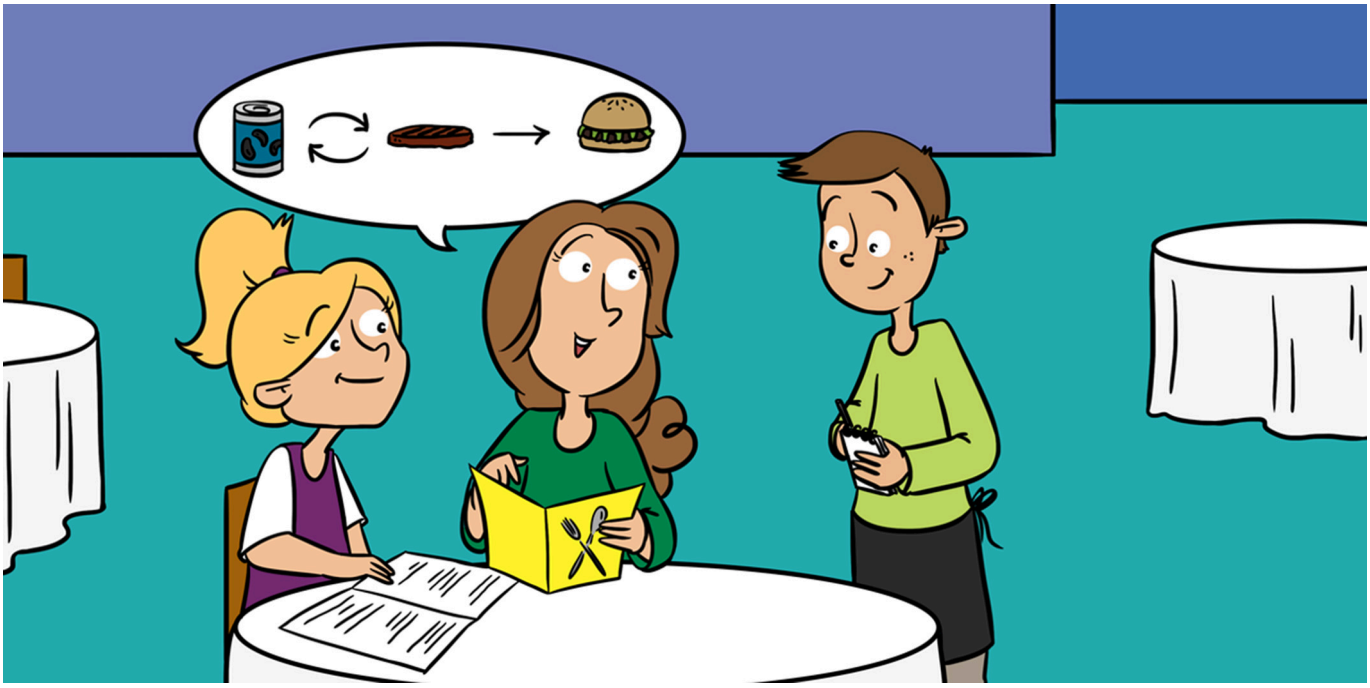

ARE RED AND PROCESSED MEATS BAD FOR OUR HEALTH?

Lieselot Y. Hemeryck[1], Sophie Goethals[2], Lieven Van Meulebroek[1], Thomas Van Hecke[2], Els Vossen[2], John Van Camp[3], Stefaan De Smet[2] and Lynn Vanhaecke[1]*

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Metabolites are substances that are formed within our bodies that help us live and grow. Examples include glucose and vitamin D. When changes happen in our bodies, like when we get sick, these metabolites can change. By studying metabolite changes, using a method called metabolomics, we can learn a lot about diseases, what causes them, and how to avoid them. We know that eating foods like fish, fruits, and vegetables is healthy. Eating too much red and processed meat, however, increases our chances of developing certain types of cancer. Unfortunately, we still do not understand why that is. It could be that there are unhealthy, toxic elements or substances in the meat itself or that there are toxic metabolites formed during or after the digestion of red and processed meat. To find out, we must journey into the gut, using metabolomics!

METABOLITES: THE LINK BETWEEN FOOD AND HEALTH?

We all know that food is essential because it provides us with the energy and building blocks necessary to live and grow. After food is chewed and swallowed, it is digested and broken down into energy and nutrients in the stomach, small and large intestines, followed by absorption. Healthy foods, like whole grains, fish, fruits, and vegetables, provide our bodies with lots of helpful substances. Unfortunately, not all foods are healthy. Certain foods can also contain harmful, toxic substances or can lead to the formation of toxic **metabolites** during or following digestion. Metabolites are the intermediate or end product of **metabolism**, involved in the chemical reactions by which your body converts food into energy. Generally, the amount of harmful metabolites in one meal is too small to instantly make us sick. But, if we eat too much of these unhealthy foods too often, long-term exposure to toxic metabolites may lead to the development certain diseases.

One example of such a disease is **colorectal cancer**. In this form of cancer, dangerous tumors form in the gut, particularly in the **colon** and the **rectum**. The risk of developing colorectal cancer is linked to family history, smoking, and an unhealthy diet and lifestyle, including eating too much red meat (like beef and pork) and processed meat (like ham, meatballs, luncheon meat, sausages, and bacon). It is important to note that eating a lot of white meat, like chicken or turkey, is not linked to colorectal cancer.

METABOLITES

An intermediate or end product of metabolism.

METABOLISM

The chemical reactions by which your body converts what you eat and drink into energy.

COLORECTAL CANCER

A form of cancer in the gut, with formation of dangerous tumors in the colon and/or rectum.

COLON

The longest part of the large intestine, connected to the small intestine at the one end and the rectum at the other.

RECTUM

The last part of the large intestine, connected to the colon at the one end and the anus at the other.

METABOLOMICS

The study of all metabolites in a cell, tissue or organism.

WHY DO RED AND PROCESSED MEATS CAUSE CANCER?

Scientists are convinced that eating too much red and processed red meat leads to the formation of harmful metabolites in the gut. We, however, still do not know which metabolites are formed exactly and how this leads to cancer. That is why we set up a study to investigate which metabolites are formed when we consume meals that contain different types of meat. This was done using **metabolomics**. Metabolomics is a method that allows us to measure the types and amounts of metabolites that are present in for example a stool sample, enabling us to observe which metabolites were formed during food digestion (Figure 1).

The study was performed using pigs. Pigs are good animals to use to study the digestion of food because the pig gut strongly resembles the human gut. In our study, pigs were fed diets with either red and processed meat or white meat (chicken) for 4 weeks in a row. After 4 weeks, samples of the pigs' gut content were collected and analyzed using metabolomics (Figure 2).

Figure 1

By means of a method called metabolomics, we can measure which and exactly how much metabolites are present in for example a stool sample. This allows us to investigate which metabolites were formed during the digestion of food (*figure created with BioRender.com*).

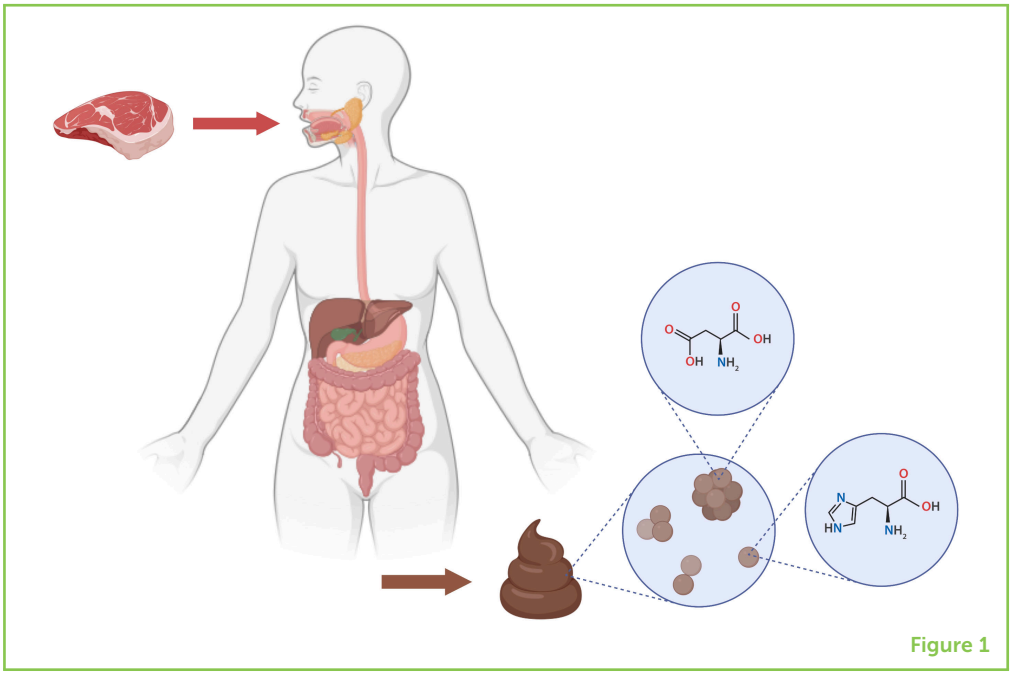
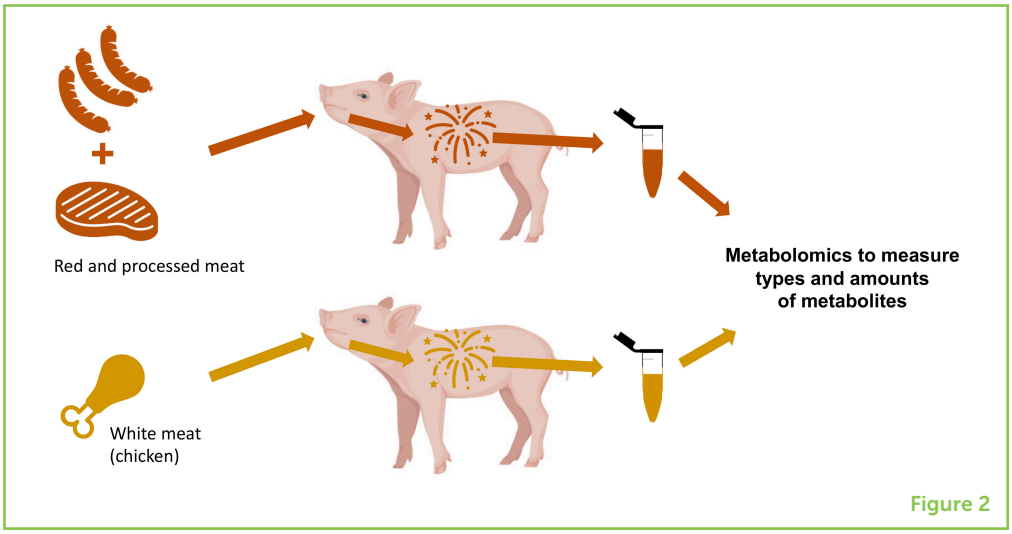


Figure 2

Pigs were used to study differences in the types and amounts of gut metabolites following 4 weeks of a diet with red and processed meats compared to a diet with white meat. Results of this experiment could help us to understand whether eating red/processed meats produces metabolites that contribute to the risk of colorectal cancer (*figure in part created with BioRender.com*).



WHAT DID METABOLOMICS TELL US?

Using metabolomics, our group discovered that the type of meat affects the types and levels of gut metabolites. Different metabolites are formed after eating red and processed meat compared to after eating white meat [1]. Some metabolites were less abundant in the pigs that ate the red and processed meat diet compared to those that ate the white meat diet, and other metabolites were more abundant. The metabolic differences we saw may be linked to differences in the composition of red/processed meat vs. chicken, but those differences may also be explained by changes in the digestive tract caused by these two types of meats, or changes in the helpful microorganisms that live in the digestive tract [2].

CARNITINE

A metabolite that plays an important role in the production of energy in cells.

LYSOPHOSPHATIDYLCHOLINES

Metabolites derived from fats.

The pig study further revealed that a metabolite called **carnitine** as well as several metabolites created from the breakdown of carnitine were higher after the consumption of red and processed meat. We already knew that carnitine levels are higher in red meat than in white meat, so it was not surprising to find higher levels of both carnitine and its breakdown products in the gut following the consumption of red/processed meat. Other gut metabolites that were higher following diets containing red and processed meat were **lysophosphatidylcholines**, which are fat-breakdown products. This makes sense because the processed meats in the red and processed meat diets (ham sausage for example) contained more fat than the lean chicken meat in the white meat diets.

THE END TO THIS QUEST: A LINK WITH COLORECTAL CANCER?

Our quest in the gut, using metabolomics, provided some interesting discoveries. We found that there was a prominent difference in the types of metabolites detected after red and processed meat consumption in comparison to white meat consumption.

It was not possible to determine whether the pigs that ate a red and processed meat diet had a higher risk of developing colorectal cancer later in life because the study only lasted for 4 weeks. However, previous studies demonstrated that elevated levels of certain carnitine breakdown products, as well as lysophoshatidylcholines, are linked to the development of colorectal cancer. Levels of lysophoshatidylcholines are increased in colorectal tumor tissue [3], and elevated levels of carnitine metabolites can be found in the blood of colorectal cancer patients [4]. Could it be that the carnitine metabolites and/or lysophoshatidylcholines are the missing link between red and processed meat consumption and colorectal cancer?

Ongoing and future scientific studies should focus on how carnitine metabolites and lysophoshatidylcholines might increase the risk of developing colorectal cancer. It could be that these metabolites attack the healthy cells in the gut, or maybe they provide nutrients for tumor cells.

SHOULD WE EAT LESS RED AND PROCESSED MEAT?

How should we apply this knowledge in our everyday lives? Based on what is known today about the health effects of red and processed meat consumption, recommendations [5] are to consume very little, if any, processed meat and to limit the consumption of red meat to no more than about three portions per week (equivalent to about 350–500 g cooked weight). This does not mean that you should

completely avoid eating meat, since meat can be a valuable source of nutrients, including high-quality protein, iron, zinc, and vitamin B12. The results of future research may further finetune these guidelines, as scientists discover exactly how the metabolites generated from red/processed meats affect our bodies. We do not know the answers yet, so there are many more quests to come!

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I am an aspiring biomedical student and love all things related to the human body. I enjoy watching crime shows that use science to solve the mystery. I have been surrounded by medical science and research my entire life. When I am not studying, I am a dancer and artist.

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Sophie Goethals is a researcher at the Flanders Research Institute for Agriculture, Fisheries and Food in Belgium. She has been fascinated by nature and by how our bodies work for as long as she remembers. During her Ph.D., she learned that humans and pigs share many physiological similarities and used pigs as a model for humans, to study what happens in our bodies when we eat meat. Currently, Sophie's work focusses on efficient pig production. Besides taking care of piglets, Sophie also really enjoys hiking and playing the tenor horn.

LIEVEN VAN MEULEBROEK

Lieven Van Meulebroek is a researcher from Ghent University (Belgium) who is currently employed at the pre-clinical CRO company ProDigest. Both during his academic career as well as at ProDigest, Lieven is very much interested in the measurement of small molecules. The biggest challenge? Picking the right strategy to achieve the most reliable measurements and go for the scientific win. This is something he also enjoys when playing board games, a hobby where creative strategies are often key.

THOMAS VAN HECKE

Thomas Van Hecke is a post-doctoral researcher at Ghent University in Belgium. Following his graduation as a veterinarian, he started his research intrigued with the question how our health is influenced by what we eat. More specifically, he is interested in what happens in the body after we eat meat. Is this affected by meat processing techniques? Do other foods or beverages influence the effects of meat consumption on health? Besides his research, he loves to travel, discover new places, and play with his 2 daughters.

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Els Vossen is a lab coordinator at Ghent University in Belgium. Els studied Bioscience engineering specialized in agriculture as she is fascinated by food production and the science behind it. She is especially interested in meat science. After work and during the weekend, she enjoys playing with her children, going out with friends, reading a book or having a nice meal.

JOHN VAN CAMP

John Van Camp is a bio engineer (1989) with a special interest for nutrition and health. He obtained a Ph.D. (1997) at the Faculty of Bio-Science Engineering (FBE) at Ghent University, Belgium, where he became nutritionist in the research group Food Chemistry and Human Nutrition at FBE-UGent. His research unit develops advanced models with animal cells to study the metabolism of bioactive components in our foods. John has a passion for science and teaching. He also likes traveling and exploring the diversity of our planet.

STEFAAN DE SMET

Stefaan De Smet is a professor in Animal Sciences at Ghent University, Belgium. He grew up on a livestock farm, which triggered his interest in understanding the role animals can play at the benefit of humans. In his research, he focuses on the qualities of foods of animal origin (meat, milk and eggs), and how these foods contribute to adequate nutrition and affect human health. In his spare time, he loves breeding and riding horses.

LYNN VANHAECKE

Lynn Vanhaecke holds an M.Sc. (2004) and Ph.D. in Bioscience Engineering (2008) and is at present Full Professor and head of the Lab of Integrative Metabolomics at Ghent University with a 20% appointment at the Institute of Global Food Security at Queen's University Belfast. The holistic analyses of small molecules through metabolomics using advanced mass spectrometry, in relation to the diet—microbiome—health axis, belong to her major research objectives. A healthy diet is a healthy life and thus a healthy metabolome!

frontiers FOR YOUNG MINDS

HUMAN HEALTH
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EAT FRUITS IN-SEASON TO GIVE RHYTHM TO YOUR LIFE

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YOUNG REVIEWER:

YOUNIS

AGE: 15

Do you think that eating fruit in summer has the same effect on your body as does eating it in winter? Scientific evidence says no. Fruits contain polyphenols, which are substances produced by plants in response to the growing conditions. When animals eat these fruits, polyphenols signal animals' bodies to adapt to the seasons. For example, bears eat berries in late summer because these fruits provide essential substances needed during hibernation. It has been observed that the effect of these fruit substances is affected by biological rhythms, which are chemical cycles that animals' bodies follow that vary throughout the year. Thus, eating fruit in- or out-of-season generates different effects in your body. Eating fruit in-season is associated with optimal health effects. Hence, we must eat fruits in-season so that the rhythms of our lives are synchronized with the seasons.

BIOLOGICAL RHYTHMS

Biological rhythms are natural cycles of changes in chemicals or functions in our bodies. The biological rhythms work as an internal "clock" that coordinates the other clocks in our bodies.

PERIPHERAL CLOCKS

Peripheral clocks reside in various tissues throughout the body, and allows organisms to optimize their behavior and metabolism to adapt to daily demands they face by tracking the time of day.

Do you think that eating a fruit in summer has the same effect on your body as does eating it in winter? Many of you will say yes, but some scientific evidence says no!

The activity of our cells, and the cells of other organisms, is not always the same—cellular activity changes depending on the time of day and the season of the year. Animals, including humans, have what are known as **biological rhythms**, controlled by internal clocks. In mammals, there is a central clock located in the brain, which produces two proteins (called CLOCK and BMAL1) that can join to form a complex (Figure 1). This complex interacts with the clock genes and activates them. The activation of clock genes creates several proteins that travel throughout the body and act as signals that regulate the functioning of the body's cells. In addition to the clock in the brain, all the cells of the body have their own clocks (called **peripheral clocks**) that control the specific processes in each organ, such as in the liver or intestines. For example, at night we produce molecules that make us sleepy, helping us to rest and recover from the day and giving us energy for the following day.

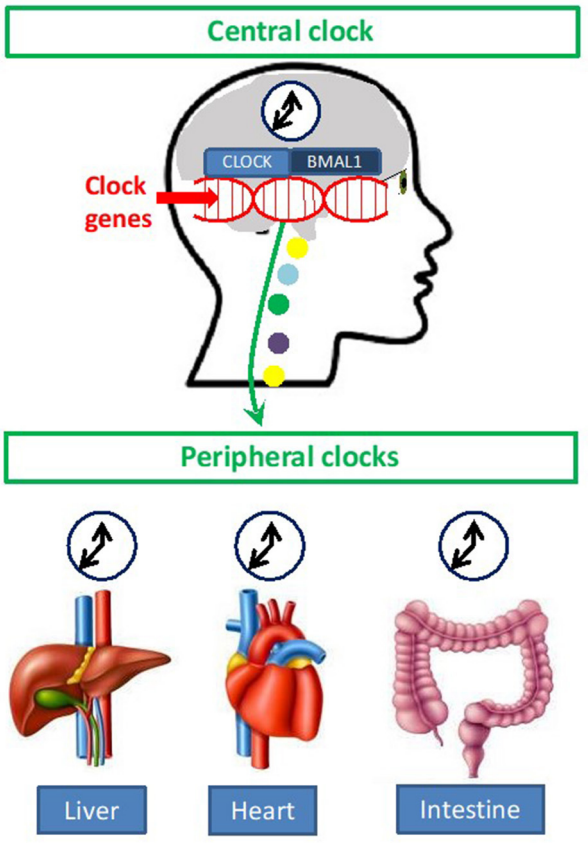

Figure 1

The body's central and peripheral clocks regulate its functions. In certain cells of the brain, the proteins CLOCK and BMAL1 join, forming a complex, which interacts with clock genes and activates them. The activation of the clock genes produces various proteins that travel to the peripheral clocks located in the organs including liver, heart and intestines. There, they act as signals that regulate the functioning of the body's cells through correct synchronization of these organs.

HOW DOES THE BODY KNOW WHAT TIME IT IS?

The body sets the time of its cellular clocks using signals such as light. But as we all know, the number of hours of light per day is not the same over the entire year. Summer days have more hours of light than winter days, for example, due to the rotation of the Earth around the Sun. In response, our bodies have evolved to use light efficiently, adjusting our functions and behaviors to this rotation and adapting to the light changes.

The activity of our cells follows two types of biological rhythms. **Circadian rhythms** explain how organisms organize their functions in 24-h cycles, while **circannual rhythms** are defined in 12-month cycles (Figure 2) [1].

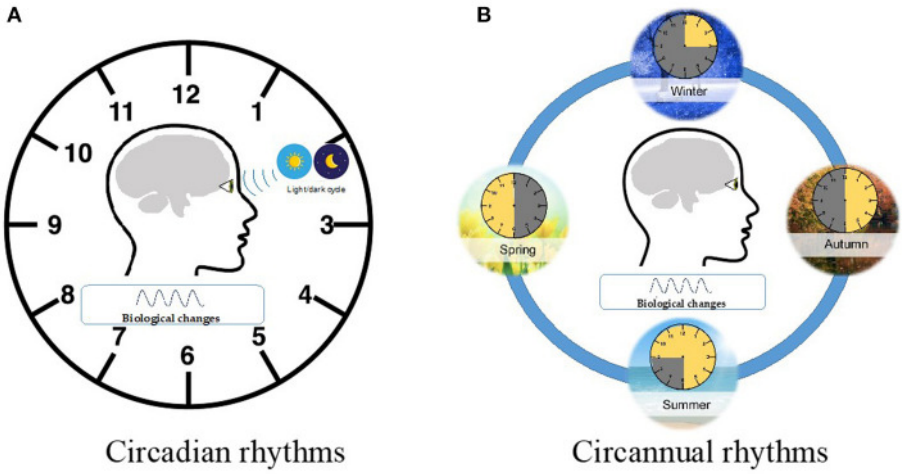

Figure 2

In addition to light, which is one of the main signals that set our biological clocks, other important factors, such as nutrition, can also affect our biological rhythms. This means that what we eat can change the way our bodies function. For example, plants contain substances that, when eaten, serve as signals that regulate our clocks. The **xenohormesis theory** proposes that some of these plant substances provide our bodies with information about the environmental conditions in which those plants were grown, and these signals allow us to adapt to the various seasons of the year. In other words, this theory says that if we consume fruits and vegetables produced where we live when they are in-season, our bodies will be ready to make the changes required to face the upcoming season. For example, bears eat berries in late summer because these fruits provide them essential compounds needed during hibernation [2].

CIRCADIAN RHYTHMS

Circadian rhythms are daily cycles of physiology and behavior that are driven by an internal clock with a period of approximately (*circa*-) 1 day (*dies*).

CIRCANNUAL RHYTHMS

Circannual rhythms are long-term (tau ≈ 12 months) cycles of physiology and behavior that are crucial for life.

XENOHORMESIS THEORY

Xenohormesis theory postulates that animals adapt to changes in environment by consuming substances produced by plants which act as signals of external conditions in which the plants were grown.

PLANT POLYPHENOLS SYNCHRONIZE BIOLOGICAL RHYTHMS

POLYPHENOLS

Polyphenols are substances produced by stressed plants in response to the growing conditions. They are present in fruits and vegetables and can lead several health effects when they are consumed.

Polyphenols are substances produced by plants that are good for our health—they help to prevent several diseases, such as high blood pressure and obesity. In addition, polyphenols can also affect biological rhythms. There are more than 8,000 different polyphenols [3], present in fruits, vegetables, cocoa, and beverages such as tea or wine. These compounds are produced by the plants in response to environmental stresses such as cold temperatures, rainfall, or drought. Therefore, each plant has a specific, unique polyphenol composition depending on the environmental conditions in which it was grown, and those polyphenols provide us with information about the environment during the plant's growing season.

But today, all fruits and vegetables can be eaten throughout the whole year. For example, the orange, a winter fruit, is grown and harvested during the winter in South Africa, and can be eaten in Europe during the spring and summer. According to the xenohormesis theory, if a European eat this orange, he will receive "winter" signals and his body will prepare for winter. This can cause a conflict, or desynchronization, between his internal clock and the actual environment conditions (Figure 3).

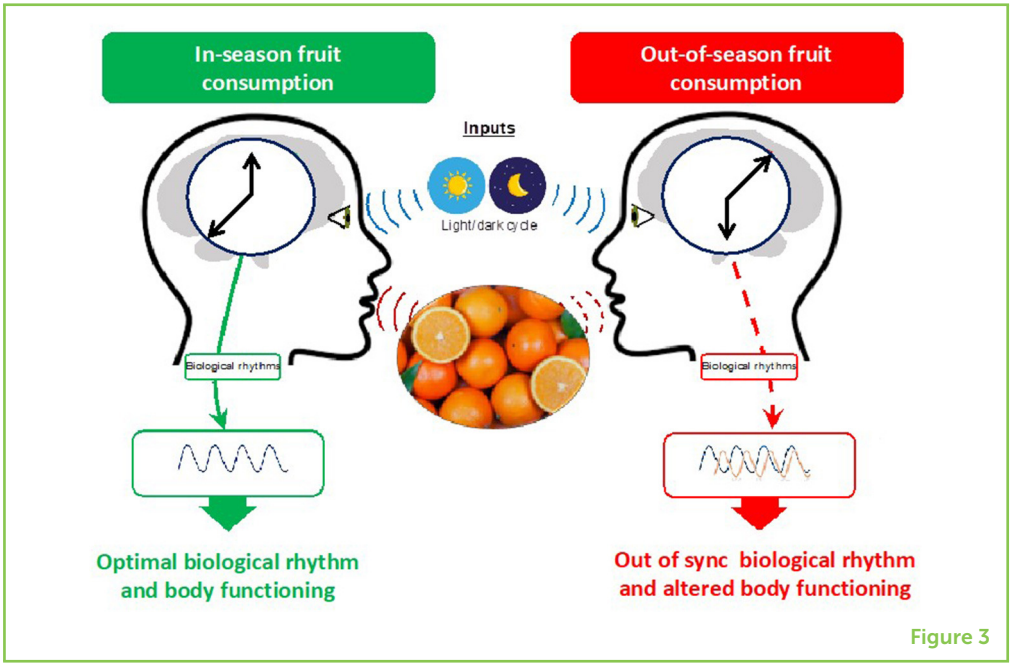

Figure 3

Consumption of polyphenol-rich fruits in-season may cause improve body functions, by synchronizing correctly the biological rhythms. However, consuming these same fruits out-of-season may result in different biological responses [Adapted from [4]].

WHAT HAPPENS WHEN I EAT FRUITS OUT-OF-SEASON?

CHRONONUTRITION

Chrononutrition is a new area of study that focuses on the interactions between biological rhythms, nutrition, and metabolism, as well as the implications for health.

Chrononutrition is the field of research that studies the interactions between biological rhythms and nutrition. Using rats, our group has evaluated the effects of eating various fruits both in- and out-of-season. To do this, the rats were adapted to different periods of light and darkness, to simulate the seasons. These periods were

either 6 h of light and 18 of dark, to simulate winter, or 18 h of light and 6 h of dark, to simulate summer. The rats were fed grapes, sweet cherries, tomatoes, and oranges. Our results showed that eating these fruits in-season enhanced the rats' body functions, by acting on the liver, muscles, and intestines, among other organs [4]. Eating the same fruits out-of-season produced different biological responses [4]. For example, when rats ate grapes in-season (winter), their intestines absorbed more polyphenols than did the intestines of rats that ate grapes out-of-season (summer).

WHAT DOES THIS MEAN FOR ME?

Since polyphenols provide health benefits, as mentioned earlier, the rats therefore obtained more health benefits from polyphenols when they consumed fruits in-season. This evidence is in line with the xenohormesis theory, and it suggests that we should eat fruits in-season, so that the rhythms of our lives are synchronized with the environment. However, it is still better to eat fruit out-of-season than not to eat fruit at all. Remember that eating five servings of fruits and vegetables (in- or out-of-season) per day is recommended but, according to our evidence, it is better to eat fruits and vegetables that are in-season.

Going back to our initial question, do you *still* think that eating fruit in-season generates the same effect as eating it out-of-season?

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YOUNG REVIEWER

YOUNIS, AGE: 15

Hi! My name is Younis, and I am 15 years old, I have always felt attracted to science subjects as they are very fascinating, especially environmental management geography geology and space. And through frontiers for young minds I hope to learn more about the world we live in.

AUTHORS

ÁLVARO CRUZ-CARRIÓN

I am a post-doc at the Arkansas Children's Nutrition Center of University of Arkansas for Medical Sciences. I am experienced in Nutrition and Metabolism. Currently, I am actively involved in projects aimed at understanding the profile of micronutrients and bioactives in foods, their interactions in food systems and how these interactions serve to modify absorption and metabolism of these compounds by humans. I think that science is universal and should be for everyone, so I

am passionate about communicating and divulging such outcomes. Contact me at ajcruzcarrion@uams.edu.

MA JOSEFINA RUIZ DE AZUA

My name is Josephine. I was born in Argentina, but I live in Spain. I am a nutritionist, I did a master's degree in nutrigenomics and personalized nutrition and I am currently a doctoral student in Nutrition and metabolism, at the URV. I study the effect of the consumption of cherries and tomatoes of different origins and their intake in different seasons. Contact me at mariajosefina.ruiz@urv.cat.

FRANCISCA ISABEL BRAVO

I am a biologist and doctor in food science and technology. Nowadays, I am a lecturer in the Biochemistry and Biotechnology Department at the Universitat Rovira I Virgili. My research is focused in obtaining compounds from food or natural sources, which could exert beneficial effects on our body and understanding how they work. The purpose is that these compounds can be useful to prevent or *delay the onset* of different diseases such as hypertension or obesity. In my spare time, I like cooking, watching series and traveling to new places franciscaisabel.bravo@urv.cat.

BEGOÑA MUGUERZA

Doctor in biology, after many years working in the food industry I moved to the academy, to the Universitat Rovira i Virgili. I now lead the Nutrigenomics Research Group, focusing our research in the study of bioactive compounds from natural sources such as polyphenols and their relation with health management and prevention. Contact me at begona.muguerza@urv.cat.

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Doctor in Food Technology, working in the Nutrigenomics Research Group (URV, Spain), I study the role of bioactives compounds under a nutrigenomic point of view. In recent years I've focused my research on the impact of biological rhythms: what and when should we eat to keep healthy? These things really intrigue me. *manuel.suarez@urv.cat

ANNA AROLA-ARNAL

I am an associate professor in Biochemistry and Molecular Biology at the Universitat Rovira i Virgili (URV), Spain. I obtained my Ph.D. degree working at the Imperial College of London, UK. I have been studying for many years the molecular mechanism by which food components, like polyphenols, exert health effects on metabolic pathologies associated with obesity like dyslipidemia and hypertension. At present we are interested in the study of the interaction of the biological rhythms with the effectiveness of functional ingredients. anna.arola@urv.cat.

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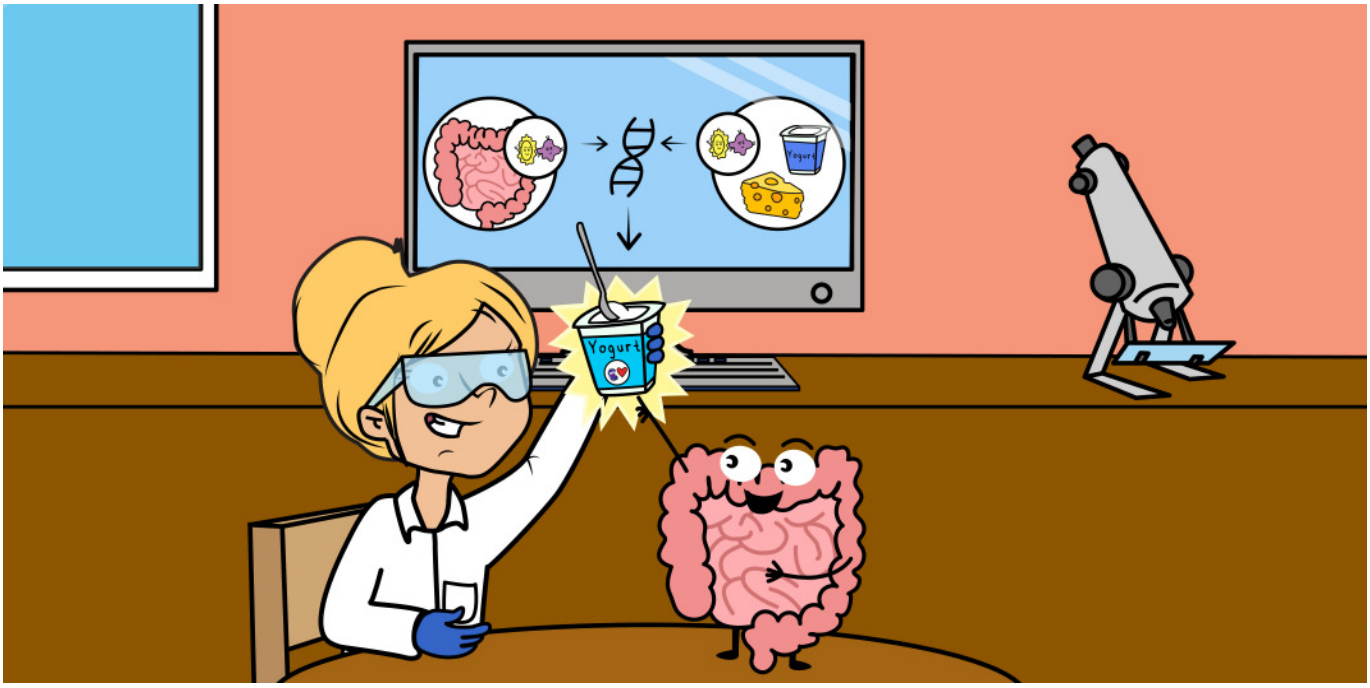

CAN EATING BACTERIA IN DAIRY PRODUCTS SUPPORT YOUR HEALTH?

Thomas Roder [1,2,3*], ***Grégory Pimentel*** [3], ***Cornelia Bär*** [3], ***Ueli von Ah*** [3], ***Rémy Bruggmann*** [1,2] ***and Guy Vergères*** [3]

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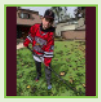
YOUNG REVIEWERS:


CAMERON
AGE: 10


ELLIOT
AGE: 11


EVE
AGE: 11

SPECIES

A group of organisms, like bacteria, that behave similarly and have very similar genomes.

Huge numbers of bacteria live in the human gut. We know those bacteria are important to our health, so we need to treat them well. We wanted to know whether it was possible to design new yogurts that can introduce special bacteria into the gut, to improve our well-being. We studied hundreds of types of bacteria isolated from cheese and yogurt and found that 24 of these bacterial species can perform most of the important bacterial functions that happen in the human gut. Therefore, there is exciting potential for designing new, gut-healthy yogurts.

BACTERIA KEEP US HEALTHY

Bacteria were among the first life forms to appear on Earth. They are extremely small organisms, consisting of a single cell. There are many **species** (major types) of bacteria that can be incredibly different from

each other: some prosper deep below the ocean, at temperatures higher than that of boiling water, while others live happily in Antarctic ice. Bacteria populate the entire surface of Earth. So, it is not surprising that some bacterial species live with humans—a vast number of bacteria live in and on our bodies. Unfortunately, humans commonly think of bacteria as bad, because some types of bacteria can make us sick. Yes, there are bad guys—but there are also good guys! In fact, most bacterial species do *not* make us sick, and some even help us stay healthy [1, 2]. Most of the bacteria that live inside humans are found in the gut. These good bacteria protect us against disease-causing bacteria, help us digest food, and produce vitamins that our bodies need but cannot produce on their own [1]. Recently, researchers found that gut bacteria can even influence mental health [1]. Together, this collection of gut bacteria is known as the **gut microbiome**.

GUT MICROBIOME

All the bacteria that live in the human gut.

WHAT MAKES A HEALTHY GUT MICROBIOME?

How can we nurture good gut bacteria without strengthening the bad ones? One way is to feed our good gut bacteria their favorite foods. Fast foods, for example, even though they are very tasty, are good neither for us nor for our gut bacteria. Fast foods are full of sugar and low in vitamins and fiber. Most good gut bacteria prefer to be fed fiber, and if there is not enough, they can starve! It is important for the gut microbiome to contain many different types of bacteria, because a high **diversity** in the gut microbiome makes us more resistant to infections and to the effects of the occasional fast-food treat. Why might that be?

DIVERSITY

The variety of living things in a particular habitat. The more species, the higher the diversity.

Suppose the bacteria in the gut are very diverse. Some like to eat sugar, some fat, some fiber, and some protein. In that case, when there is no sugar around, only the sugar-eating bacteria become weak—the others are fine, which means that, as a whole, the community is still strong. However, if most bacteria only ate sugar, the microbiome would become weak in the absence of sugar, making it much easier for bad bacteria to conquer the gut and cause illness. This is one reason why a balanced diet is important.

There is another reason why a lack of diversity in the gut microbiome may be bad. When gut bacteria are diverse, multiple types of bacteria can perform the same job in the bacterial community, like digesting milk sugar or vitamin production. If one species of bacteria is lost, another might be able to take its place. In a less diverse gut microbiome, this might not be possible, and the gut microbiome may be weakened. One strategy for strengthening the gut microbiome, and thus human health, could be ensuring that there are several different bacterial species that can perform the same functions. We can achieve this by supplementing those bacteria through our diets.

CAN YOGURT OR CHEESE SUPPORT THE GUT MICROBIOME?

Bacteria can be found in many foods, particularly in dairy products like cheese or yogurt, which have been consumed for ages. Ten thousand years ago, when most people still lived as hunter-gatherers, all humans were lactose intolerant, which means they could drink milk when they were young, but if they did so as adults, they would feel bloated and sick. When humans started farming sheep, cows, and other milk-producing animals, they discovered ways to process milk so that it tasted different, lasted longer, and, most importantly, could be digested without making them feel sick [3]. We call this process **fermentation**, and it led to the production of the first yogurts and cheeses. What these early communities did not know was that bacteria were responsible for fermentation. Specific species of bacteria live and grow in milk, changing its taste, texture, and composition. After fermentation, a cup of yogurt (200 g) contains more bacteria (at least 20 billion) than there are humans on Earth (8 billion)!

FERMENTATION

The production of foods such as yogurt, cheese, bread, kimchi, beer, and wine with the help of yeast or bacteria.

Early yogurts contained many distinct species of bacteria, and every yogurt was different. In contrast, most modern yogurts only contain two species of bacteria, selected for fast and reliable mass production. Could we make yogurt from a different cocktail of bacteria, optimized not just for mass production but also to help the gut microbiome and improve human health (Figure 1)?

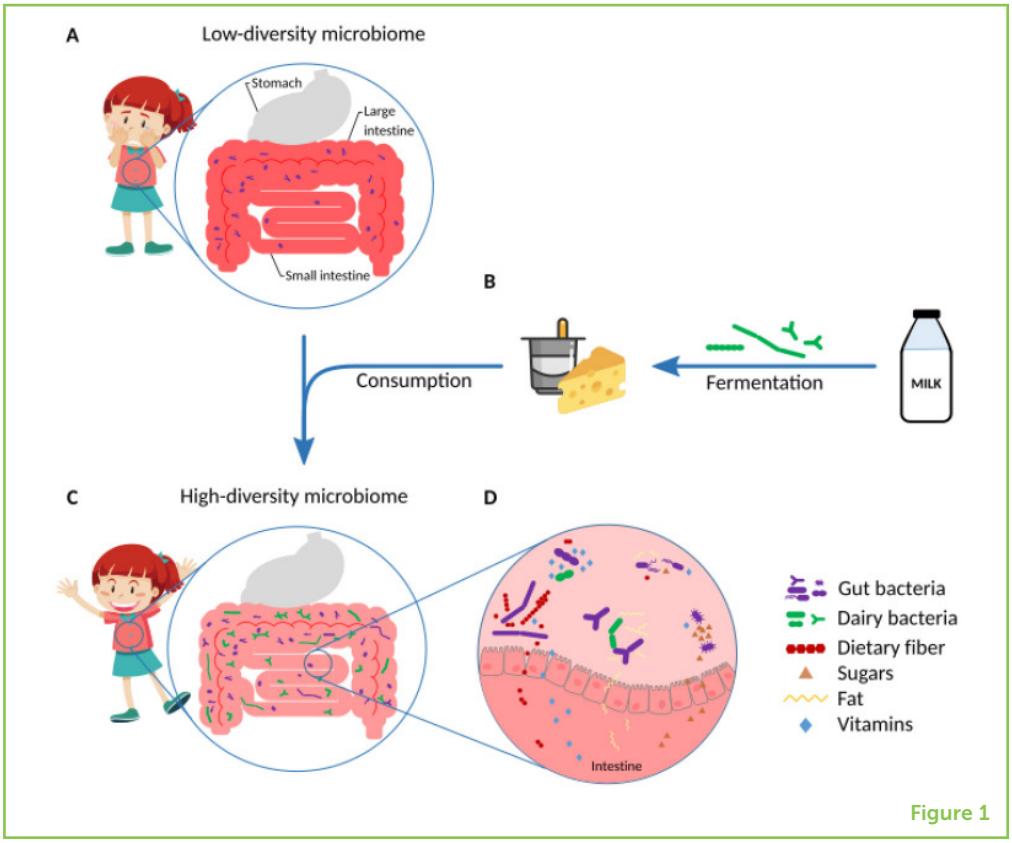


Figure 1

Figure 1

Can yogurt or cheese support the gut microbiome? **(A)** Unbalanced diets can lower the diversity of the gut microbiome, meaning that some species are present in very low numbers or even extinct. This can reduce the strength of the gut microbiome. **(B,C)** We are trying to find out if a dairy product fermented with selected bacteria can support or restore the functions of a healthy gut microbiome. **(D)** These functions include providing us with useful vitamins, sugars, and fats, and helping us to digest fiber from fruits and vegetables.

THE QUEST FOR THE RIGHT BACTERIA

Where could we get suitable bacteria for making gut-healthy yogurt? Switzerland has a proud tradition of cheese and yogurt making. Agroscope, the Swiss center of excellence for agricultural research, collects, stores, and investigates the bacteria found in yogurt and cheese. So far, Agroscope has collected over 10,000 different bacteria from dozens of species!

With such a large bacterial bank, how do we decide which are the best for a healthy yogurt? Conveniently, scientists at Agroscope have studied the DNA of close to 1,000 of the bacteria they have collected, using a process called **sequencing**, to see which **genes** the bacteria have. Genes are short segments of DNA that code for functions that allow bacteria to survive. For example, certain genes enable bacteria to split into two, and others give them the ability to swim around.

SEQUENCING

The process of studying the DNA composition of an organism.

GENE

A segment of DNA that determines a specific characteristic, capability, or function of a life form.

SUPPLEMENTING THE GUT MICROBIOME

Our idea was to see if yogurt bacteria could support gut bacteria in their work, and possibly even increase the diversity of the gut microbiome. We used DNA sequences from four human microbiomes, which contained a mix of genes from many different gut bacteria. Then, we used a computer program to determine the functions of these genes, using the same method we used for the dairy bacteria (Figure 2).

When we compared the dairy bacteria to bacteria from the human microbiome, we were surprised: each individual bacterial species from the milk could perform about half of the functions of the human gut microbiome, even though dairy bacteria are from a completely different environment and are rarely found in the human gut. Combined, our 24 species of dairy bacteria covered 89% of the functions of the human gut microbiome [4]! We also noticed that some human microbiomes lack certain functions compared to other human microbiomes. Some of those functions are present in dairy bacteria, meaning we may be able to develop a yogurt that can supplement missing or lost functions in a human microbiome, making it more resilient and thus helping people to be healthier.

WHAT IS NEXT?

Our study shows that bacteria from cheese or yogurt have similar functions to those of human gut bacteria. We think this knowledge will be very useful. For example, people with certain diseases, like obesity, lack specific types of gut bacteria. So, in future studies, we could recruit study participants with a known disease who lack the gut bacteria

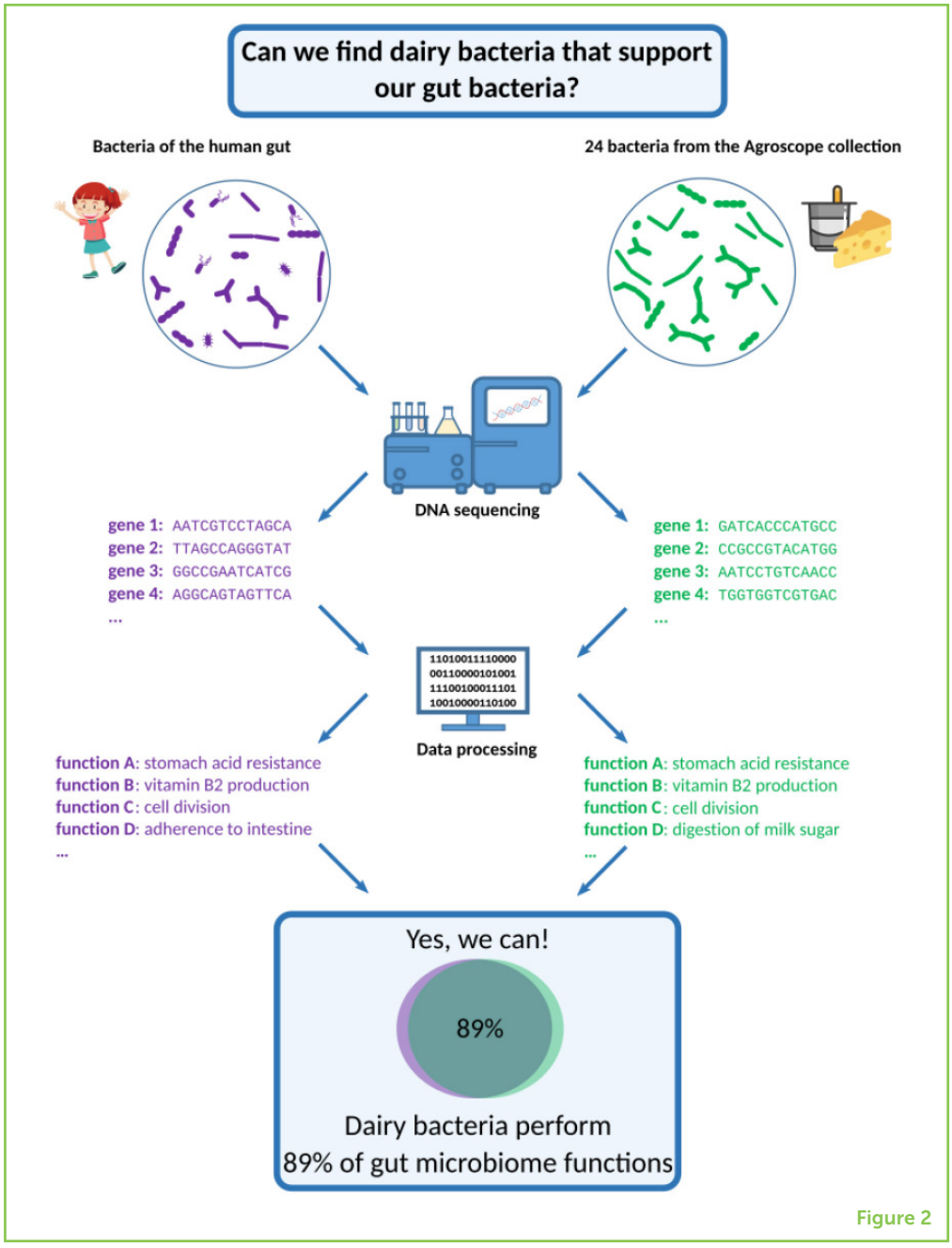


Figure 2

The quest for the right bacteria. Using DNA sequencing followed by computer analysis of the data, we found that 24 dairy bacteria from Agroscope's bacteria bank (right) can perform most of the functions of the human gut microbiome (left). This finding may help us to design a yogurt that supports the functions of the gut microbiome, making it more resilient and thus promoting human health.

that perform certain functions. Then we could search Agroscope's collection for milk bacteria that have the missing functions and produce a special yogurt with them. Next, we could feed this yogurt to the participants and evaluate the effects on their health.

Humans have been raising cattle and eating fermented foods for millennia, but only recently have we gained the understanding and the tools to develop health-promoting dairy foods based on scientific data. This process is long, but worthwhile! If scientists continue to explore the potential of bacteria to improve human health, we may eventually be able to help many people with diseases like

obesity and diabetes by feeding those people foods that contain helpful bacteria.

FUNDING

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

CAMERON, AGE: 10

I am 10 years old, I like to play sports, especially hockey. I like to read and play video games in my spare time. In the summer I like going to my cottage to swim and play baseball with my friends.

ELLIOT, AGE: 11

Elliot loves to read, play soccer and camp with his boy scout troop. He also has a blast going on adventures with his friend, Eve. Together, they like to rock climb, complete high ropes courses and downhill ski. Basically, they like to play hard and laugh hard!

EVE, AGE: 11

Eve loves to read, play softball and hang out with her friends. She also has a blast going on adventures with her friend, Elliot. Together, they like to rock climb, complete high ropes courses and downhill ski. Basically, they like to play hard and laugh hard!

AUTHORS

THOMAS RODER

Thomas is a Ph.D. student in bioinformatics at the university of Bern, Switzerland. He is trying to design new yogurts by combining various bacteria. At the same time, he is developing a website that makes comparing bacterial genomes easier. He works on these projects using computers, but prior to this project, he studied the interaction between plants and root-eating larvae in the lab. *thomas.roder@bioinformatics.unibe.ch

GRÉGORY PIMENTEL

Grégory is a researcher at the Functional Nutritional Biology Group at Agroscope. He specializes in the analysis of dairy products and other biological fluids (blood or urine) using a technique called metabolomics, which allows the detection of thousands of small compounds present in a sample. Metabolomics can help scientists better understand the chemical reactions happening in milk during fermentation, and it can be used to investigate the health effects of eating fermented dairy products. Grégory holds master's degrees in food science, engineering, and nutrition, and his Ph.D. is from the University of Lausanne in Switzerland, in cardiovascular biology and metabolism.

CORNELIA BÄR

Cornelia is a scientist in the Biochemistry of Milk and Microorganisms group at Agroscope, Switzerland. She was always driven by the desire to put scientific knowledge into practice and she earned her Ph.D. studying fortified foods. A postdoc studying food composition followed, which sparked her interest in how bacterial metabolism changes the composition of food. Trained in microbiology, immunobiology, and protein biochemistry, Cornelia is particularly interested

in which bacteria and proteins are responsible for food transformation, how bacteria interact in food, and how the consumption of these foods affects human health.

UELI VON AH

The combination of technology and biology has always been of great interest to Dr. Ueli von Ah. After studying food sciences, he earned a Ph.D. in food biotechnology. His work focuses on the use of lactic acid bacteria in food applications. In addition to finding the optimal growth conditions for these bacteria, he is also interested in understanding how genome information relates to the functions of bacteria in food. Ueli von Ah is now head of the Biotechnology research group at Agroscope, and he teaches a class in food biotechnology at a Swiss university of applied sciences.

RÉMY BRUGGMANN

Rémy is the head of the Bioinformatics Unit and director of studies of the master's of science program called Bioinformatics and Computational Biology at the University of Bern. A molecular biologist by training, he has always been interested in computer science, and in bioinformatics he found the ideal combination of his two passions. He has sequenced hundreds of genomes from bacteria and higher organisms and wants to better understand how genomic information is translated into a functioning organism.

GUY VERGÈRES

During the last three decades, Dr. Guy Vergères conducted research in several scientific disciplines, including chemistry, biochemistry, molecular biology, physical chemistry, pharmaceutical sciences, and microbiology—always with the aim of linking important molecules to their impact on human health. This combination naturally led him to conduct nutritional research on fermented foods. Guy Vergères is now heading the Functional Nutritional Biology research group at Agroscope and teaching the science of nutrigenomics (modern nutrition research) at Swiss universities.

frontiers FOR YOUNG MINDS

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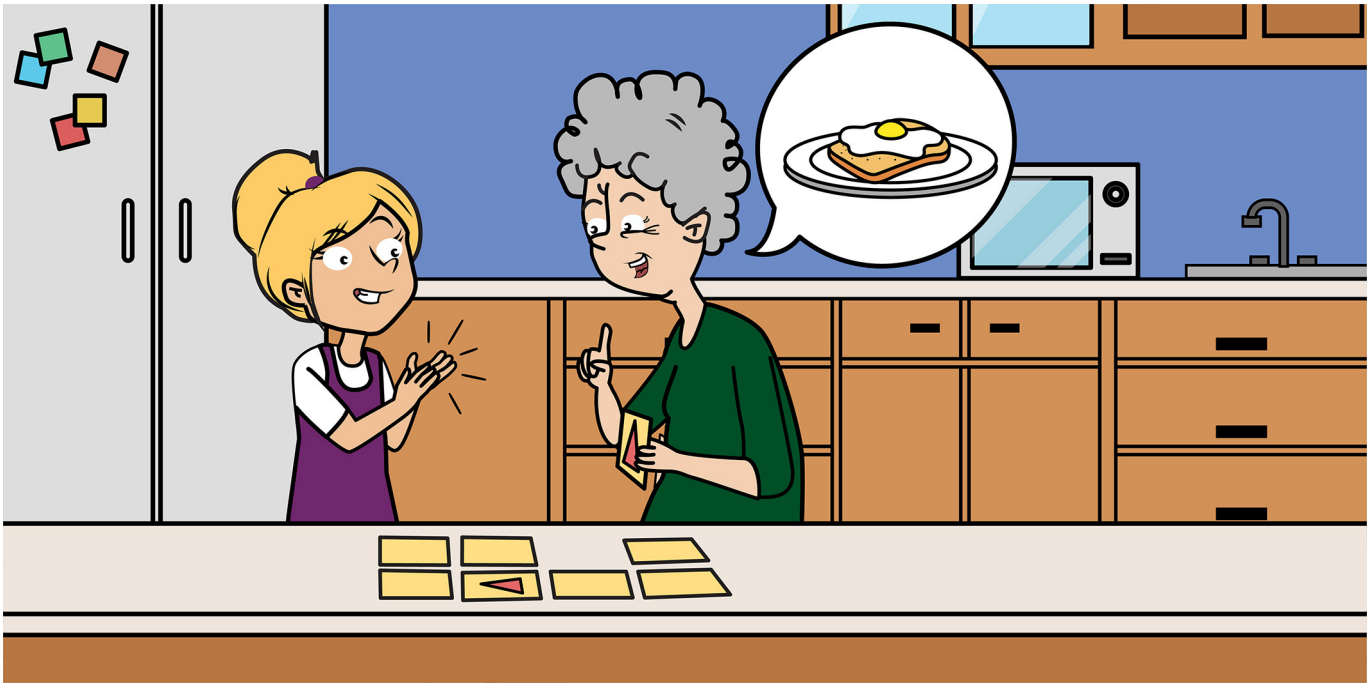

ARE EGGS A SUPERPOWER FOR THE BRAIN AND MEMORY?

Maija P. T. Ylilauri * ***and Jyrki K. Virtanen***

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YOUNG REVIEWER:

ATIF HUSSAIN

AGE: 12

When you and your friends get old, gray, and wrinkly, it is likely that some of you will end up having memory problems. The most common illness of the memory is called Alzheimer's disease. Alzheimer's causes difficulties with remembering the names of your friends, the jokes that were just told, or even the well-trodden way home. Sounds awful, right? As there is currently no cure for Alzheimer's disease, researchers are trying hard to find ways to prevent it. A healthy diet may be one approach. This article describes the potential link between eating eggs and the chance of having memory problems later in life. Maybe you are wondering how on Earth eggs and memory are connected. That is a good question! Please keep reading to find out whether eggs have superpowers for your brain and memory.

WILL YOU BE A MASTER OF THE MEMORY GAME WHEN YOU ARE OLDER?

We predict that you can easily beat your parents at a memory game! Kids are fast learners, and they remember things easily. When you get older, it may not be so easy anymore. By "older" we mean very old, when you have a wrinkly face and gray hair.

MEMORY DISORDER

An illness of the brain that causes various symptoms, including memory loss.

ALZHEIMER'S DISEASE

The most common memory disorder.

It is normal to slow down a bit when you age. Many people, however, get an illness that causes them to lose their memories little by little. This kind of illness is called a **memory disorder**. You may even know someone who suffers from a memory disorder such as **Alzheimer's disease**. That person may have difficulty recognizing you, or he or she may forget what you just said or may behave in strange ways. Those are some of the symptoms of brain and memory disorders, and they make it hard for the older person to manage in everyday life.

Sadly, we do not yet have a cure for memory disorders like Alzheimer's disease. We only have some medicines to slow down the speed of memory loss, but we do not have pills or treatments to bring back the lost memory. So, we are very keen to do everything we can to stop these disorders from happening in the first place. If you want to put up a reasonable fight against your grandkids at a memory game in the future, please keep reading!

THINGS THAT YOU EAT CAN IMPACT YOUR MEMORY

Even though a cure for Alzheimer's disease and other memory disorders does not yet exist, you can help to prevent these disorders by your choices. For example, eating a healthy diet may help your brain [1]. So, keep eating your veggies, have regular mealtimes, and save the sweets for special occasions. If your parents make you healthy foods and you eat them, you may have a better chance of keeping your mind sharp in the future.

However, this is more complicated when we consider particular food items, such as milk, tomatoes, ham, or seeds. Which foods are healthy brain foods? This is a difficult question—we do not actually know which specific foods are the best ones to maintain good memory and brain health. We are not even sure if there are specific foods that might speed up memory loss! This is something that researchers, including us, are trying to find out.

EGGS—A TRICKY FOOD!

Eggs have long been a mystery when it comes to healthy eating. You may have heard someone say that eggs are unhealthy and that you should avoid eating them, but maybe you know other people who eat

Figure 1

Eggs are full of healthy substances and may have an impact on the brain.

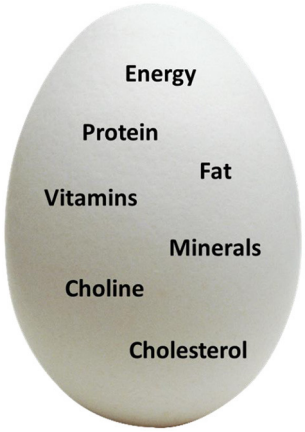

Figure 1

CHOLESTEROL

Cholesterol is a type of fat that your body makes. You may also get it from food, such as eggs or meat. Too much cholesterol in your body is not good for your heart or your brain.

APOE4

A gene that increases one's chance of getting a memory disorder. Too much cholesterol in the diet may not be good for people with this gene.

NUTRIENTS

Nutrients are substances that you need to get from food, such as carbohydrates, proteins, fats, vitamins, and minerals.

eggs every day and claim that eggs have health benefits. Well, are eggs bad for you or not? Who do we believe?

One thing that makes eggs tricky is that they have a lot of **cholesterol**. Cholesterol is a type of fat. Some people may develop diseases if they have too much cholesterol in their diets. This may happen if they inherited a gene called **APOE4** from their parents [2]. However, most people can eat some eggs without anything bad happening to their health [3–5]. Eggs are not just packages of cholesterol; they are also a very good source of many important nutrients. **Nutrients** in foods are substances that you need to grow and stay healthy. Eggs contain high-quality protein, good-quality fat, vitamins, and minerals. Eggs are also a very good source of a nutrient called choline, which may be important for brain health (Figure 1). Even though this sounds pretty good, no one has ever investigated what eggs do to our chances of getting memory disorders. So, when thinking of brain health, are eggs bad, good, or just an ordinary food?

COULD A 30-YEAR FINNISH STUDY GIVE US ANSWERS?

As far as we know, no one had ever studied whether eggs have a link with memory disorders. We were also interested in discovering whether eggs could help the brain to perform its tasks, like think and memorize. Would eating eggs help people to complete those tasks, or would eggs make it harder? And would people with the *APOE4* gene have more difficulties with the tasks if they ate more eggs? You may remember that eggs may not be good for people with that gene. Luckily, we had a lot of data available, waiting for us to dig in and find out!

Over 30 years ago, some Finnish researchers studied about 2500 middle-aged men from Finland [6]. The men were examined by doctors and study nurses. The men also gave blood samples and the

lab workers checked whether they had the *APOE4* gene. Some of the men also did brain tasks, so researchers could see how well their brains and memories worked. Then, the men kept **food diaries** for 4 days, meaning they wrote down everything they ate and drank. Based on the food diaries, the researchers could count what the men had eaten. For example, they could count the number of eggs and the amount of cholesterol in the men's diets.

FOOD DIARY

A research method used to study nutrition. Every item of food and drink is written down, as is the amount and brand name.

After 30 years, the men in that study had become very old. Some of them had developed diseases like heart disease or Alzheimer's disease, and some of them had died. We investigated whether there was a link between the number of eggs and the amount of cholesterol the men ate and memory disorders. We also investigated whether eggs and cholesterol were related to the men's performance in the brain tasks.

SO WHICH IS IT—ARE EGGS BAD OR GOOD FOR THE BRAIN?

After many computer calculations, we learned that eating one egg per day had no effect on the memory. Likewise, eating cholesterol was neither good nor bad for the memory, even for men with *APOE4*. So, in this study, it seems that eggs were neither bad nor good. When we say "in this study," we mean that the results may only be true in the Finnish study population. If we want to know whether the results hold true elsewhere, we need to do more studies in different study populations, such as women and people from other countries.

But hold on! Even though eggs seemed to be neither bad nor good for memory, they might be more than just an ordinary food. We saw that those men who ate more eggs were slightly better at completing some brain tasks compared to the men who ate fewer eggs. So, it may be that eating eggs benefits brain function, but we need to do more studies to know for sure. The take-home message of this study is that it is at least safe to eat eggs as part of a healthy diet.

KNOWN SUPERPOWERS FOR THE BRAIN AND MEMORY

So, if eggs do not turn out to be a superpower for the brain and the memory, what is? Lots of research is happening on this topic, but some things are already to known to help keep the brain fresh and nimble.

- Use your brain! Be active at school, do your homework, and keep playing games.
- Exercise! It does not matter whether you go to a sports club or play football with your friends. Everything counts!

- Protect your brain! If you ride a bike or a horse, always wear a helmet.
- Eat healthily! A healthy diet contains a lot of vegetables, fruit and berries, whole-grain cereals, vegetable oils, and moderate amounts of animal products. Don't worry, a healthy diet can contain some sweets too, if most of the other recommendations are met.

Practice these tips and your brain will have many healthy years ahead!

ORIGINAL SOURCE ARTICLE

Ylilauri, M. P. T., Voutilainen, S., Lönnroos, E., Mursu, J., Virtanen, H. E., Koskinen, T. T. et al. 2017. Association of dietary cholesterol and egg intakes with the risk of incident dementia or Alzheimer disease: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am. J. Clin. Nutr.* 105:476–84. doi: 10.3945/ajcn.116.146753

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YOUNG REVIEWER

ATIF HUSSAIN, AGE: 12

A caring, fun loving kid plays football and wishing to become austronaut; who brings smiles on everyone's face.

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I am a registered dietitian and an early-stage researcher at the University of Eastern Finland. I am finishing my doctoral studies on nutritional epidemiology. I have been studying the associations of dietary factors with risk of memory illnesses and with brain performance. When I am not working, I like doing various sports, such as cross-country skiing, weight training, jogging, and cycling. I also read both non-fiction and fiction. My husband and I have two brilliant young scientists of our own, an 9-year-old son and a 5-year-old daughter. *maija.ylilauri@uef.fi

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Like Maija, I am a registered dietitian. I am working as an associate professor of nutrition and public health at the University of Eastern Finland. My main research interests revolve around major chronic diseases, such as cardiovascular diseases, type 2 diabetes, and memory disorders. I study how we can affect the risk of those diseases with a healthy diet. At home, I have a young Danish mastiff dog who keeps my wife and our 11-year-old daughter busy. When I have some free time, I like to go to the gym, mountain biking, cross-country skiing, or horseback riding.

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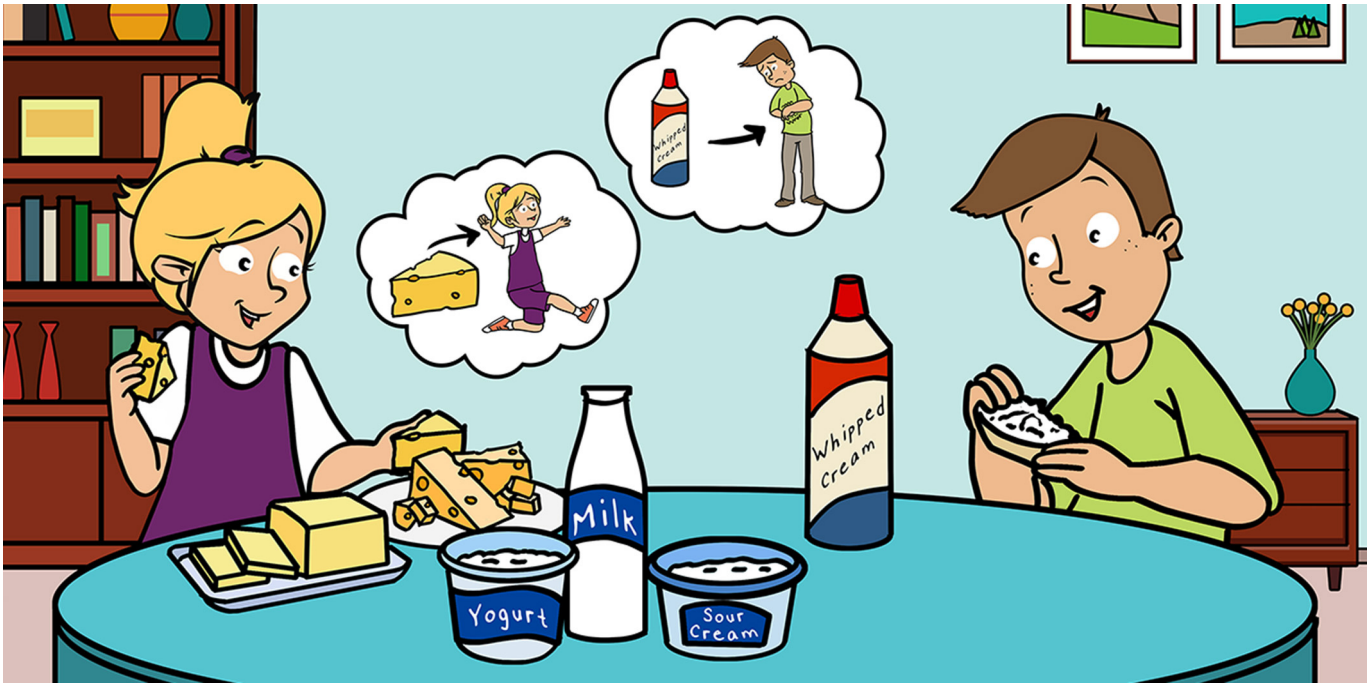

DOES IT MATTER WHAT KIND OF DAIRY PRODUCTS WE EAT?

Amanda Rundblad[1*], Kirsten B. Holven[1,2], Linn K. L. Øyri[1], Patrik Hansson[3], Ingvild H. Ivan[1], Gyrd O. Gjevestad[4], Magne Thoresen[5] and Stine M. Ulven[1]

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Dairy is important in many people's diets. Although all dairy products are made from cow's milk, various dairy products are made by different processes. This means that they can end up having different nutrients and properties. Researchers and nutritionists usually group all dairy as one food group, but this might miss information about the health effects of eating different dairy products. Immune cells are important to protect us when we get sick. Sometimes, immune cells can be turned on for the wrong reasons and cause too much inflammation, which can lead to diseases. We studied immune cells from people who ate meals with either butter, cheese, whipped cream, or sour cream. After eating cheese and sour cream, immune cells showed fewer signs of inflammatory processes than after eating

YOUNG REVIEWERS:

AMAYAH
AGE: 16

KAY
AGE: 13

butter and whipped cream. This may mean that cheese and sour cream could be healthier than butter and whipped cream.

DAIRY—MANY DIFFERENT PRODUCTS MADE FROM THE SAME MILK

Many people eat dairy products every day. Milk, cheese, cream, butter, yogurt, and sour cream have very different tastes and textures, but they are all made from cow's milk. Bacteria are added during the production of some dairy products, like cheese, yogurt, and sour cream, to start a process called **fermentation**. Such products are called fermented dairy products. Dairy fermentation involves adding bacteria to milk. The bacteria break down the milk sugar and, in the process, create a waste product called lactic acid. The lactic acid produced by fermentation gives these products their sour taste. Fermentation may also produce other molecules that can affect our health.

Are dairy products healthy? This is actually a difficult question to answer [1]. On one hand, dairy foods are a great source of protein, calcium, potassium, and vitamins B2 and B12. These nutrients ensure healthy growth and development of muscles, bones, and the **immune system**. On the other hand, many dairy products, like butter, cream, cheese, and sour cream contain a high amount of fat. About 65% of this fat is **saturated fat**. Eating too much saturated fat increases levels of "bad" cholesterol, called LDL-cholesterol, and may also cause **inflammation.** Both LDL-cholesterol and inflammation contribute to the development of heart disease, also known as **cardiovascular disease** (**CVD**).

HOW ARE IMMUNE CELLS INVOLVED IN HEART DISEASE?

CVD is the main cause of death worldwide [2], however, it is a disease that can mostly be prevented by having a healthy lifestyle. The most common effects of CVD, like heart attacks, are caused by **atherosclerosis**. Atherosclerosis is a build-up of LDL-cholesterol and other fats on the insides of blood vessel walls (Figure 1), forming what are called **plaques** [3]. This build-up attracts cells of the immune system, which enter the vessel wall and eat LDL-cholesterol, the same way that they eat other threats to the body, like viruses and bacteria. As the plaque gets bigger, the immune cells send out inflammatory signals to attract even more immune cells to help. This makes the plaque inflamed, similar to a pimple. Eventually, the plaque may burst and clog up the blood vessel, which may partly block the blood flow and make it more difficult for the heart to work properly. Sometimes the flow of blood to the heart can be completely blocked, which causes a heart attack.

FERMENTATION

A process where sugar is broken down without the use of oxygen into end products like alcohol or lactic acid. Bacteria produce lactic acid during fermentation of dairy products.

IMMUNE SYSTEM

A network of different cells and molecules that has the very important job of protecting us from pathogens such as virus and bacteria.

SATURATED FAT

Fat molecules without any double bonds between carbon atoms. High amounts of saturated fat is found in meat, dairy, and tropical oils like coconut and palm oil.

INFLAMMATION

The process where the immune system is fighting and trying to eliminate a threat to the body, like virus or bacteria.

CARDIOVASCULAR DISEASE (CVD)

Diseases of the heart and blood vessels. The most common forms of CVD, like heart attacks, are caused by atherosclerosis.

ATHEROSCLEROSIS

The process where fats, like cholesterol, accumulate in blood vessel walls. Immune cell also enter the vessel wall to eat the cholesterol.

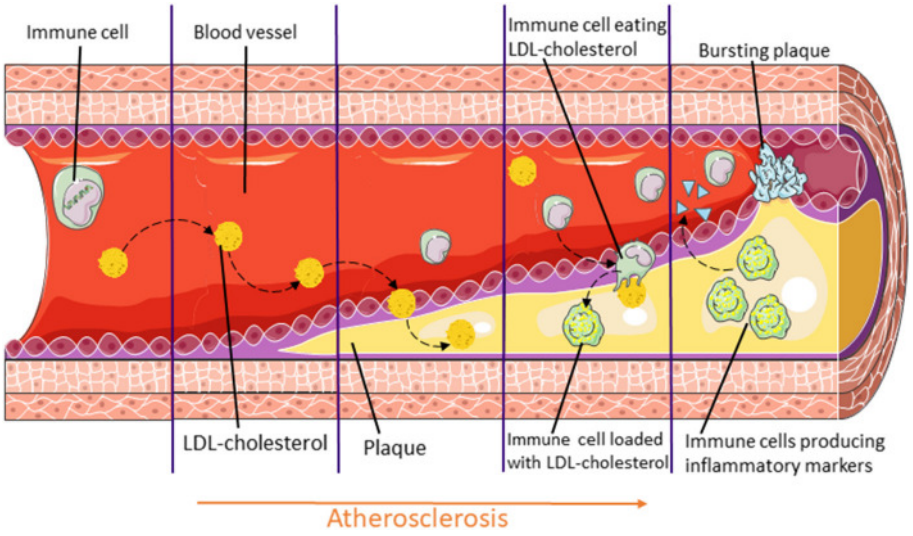

Figure 1

In atherosclerosis, LDL-cholesterol ("bad" cholesterol) and immune cells enter blood vessel walls and form build-ups called plaques. Immune cells eat LDL-cholesterol and cause inflammation of the plaque. Eventually, the plaque may burst, which can block the blood vessel and could cause a heart attack.

GENES AND PROTEINS

DNA is like a cookbook, and genes are the different recipes for specific proteins. Cells do not need all genes at all times. However, when a cell needs a gene, it can make a copy of that specific recipe. This copy is called **messenger RNA** (**mRNA**). The copy of the needed protein recipe is sent to the part of the cell that makes proteins. When the cell no longer needs the protein, the mRNA is broken down. Therefore, by measuring the levels of different mRNAs, we can see which proteins a cell is currently making, which gives us information about the processes that are active within a cell. Proteins have many different functions in the body, like speeding up chemical reactions, supporting the shape of cells and tissues, and sending signals from one place to another. Many of the proteins produced by immune cells are involved in inflammation.

PLAQUE

The site of cholesterol and immune cell accumulation inside the vessel wall. As atherosclerosis continues, the plaque becomes bigger and more inflamed, like a pimple.

Messenger RNA (mRNA)

A copy of a gene in the DNA. The mRNA carries the information about how to make a protein from the recipe in DNA to the cell machinery that makes proteins.

WHAT DOES EATING FERMENTED DAIRY PRODUCTS DO TO OUR IMMUNE CELLS?

We asked whether eating fermented or non-fermented dairy products affects the mRNA levels in immune cells. We wondered whether different dairy products would have different effects on inflammation, which, as you now know, is a key process in CVD. To study this, healthy participants were fed one of four different meals, made up of four different high-fat dairy products [4]. Two of the meals included non-fermented dairy products: butter and whipped cream. The other two included fermented dairy products: cheese and sour cream. We took blood samples from the participants before they ate anything. Then, they ate one of the four types of dairy meals. A few hours later, we took blood again. We collected immune cells from the blood samples and studied the cells' mRNA. We also measured the blood

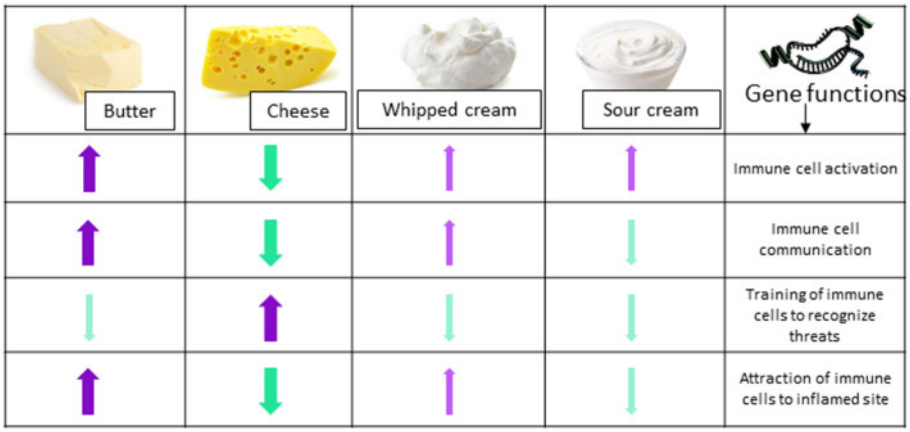

Figure 2

Changes in mRNA levels after eating the four meals are shown with colored arrows. Up-arrows show increases in mRNA and down-arrows show decreases. Stronger colors and bigger arrows indicate bigger differences. Each row shows which mRNAs were studied. These results told us that after the participants ate the fermented dairy products (cheese and sour cream), their immune cells were less active in inflammatory processes than after eating the non-fermented products (butter and whipped cream). This may mean that fermented dairy is healthier than non-fermented dairy.

levels of inflammatory signals and amino acids, the building blocks of proteins.

We found changes in mRNA levels depending on which dairy products the participants ate (Figure 2). We saw that the number of mRNA molecules for proteins involved in inflammation increased after eating non-fermented dairy products and decreased after eating fermented dairy products. For example, the mRNA for proteins that activate immune cells and attract them to the site of inflammation decreased after participants ate the cheese meal. The same was true of mRNA for proteins involved in immune-cell communication. Communication-related mRNA *increased* after the participants ate the butter meal. This means that the immune cells were more active in inflammatory processes after the butter meal than after the cheese meal. We also found that, after eating the butter and whipped cream meals, the level of inflammatory signals in the participants' blood increased.

DOES THE HIGH PROTEIN CONTENT OF CHEESE LOWER INFLAMMATION?

Cheese contains more protein than the other dairy products that we tested. When we eat proteins, they are broken down into their amino acid building blocks. This breakdown happens in the stomach and intestine, and the amino acids are absorbed into the blood. From Figure 3, we can see that the amino acid levels in the blood increased more after eating cheese than after eating the other dairy products. We also saw that, when amino acid levels increased, levels of the mRNAs we analyzed also increased. Similarly, when amino acid levels decreased, mRNA levels decreased. We cannot be sure that the changes in amino acids *caused* the changes in mRNA levels, but the amino acid changes may be *linked* to the mRNA changes. This result tells us it is possible that the high protein content in cheese may

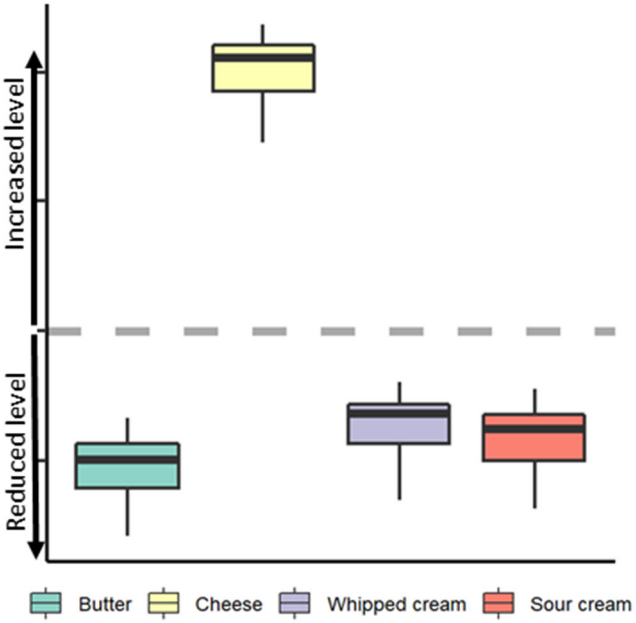

Figure 3

Change in the levels of amino acids in blood after eating four different dairy products. The dotted line represents no change. Boxes above the line show an increase, and below the line a decrease. Levels of amino acids increased after participants ate cheese but decreased after eating the other dairy products. The dark line inside each box indicates the average change in the whole group of people, and the lines coming out of the top and bottom show the largest and smallest changes for each meal.

contribute to the lower levels of inflammatory gene mRNA seen after eating cheese compared to the other dairy products.

ALL DAIRY PRODUCTS ARE NOT EQUAL

To summarize, after the participants ate the fermented dairy products, their immune cells were less active in inflammatory processes than after eating the non-fermented products. This may mean that fermented dairy is healthier than non-fermented dairy. The difference in nutrient content of different dairy products, such as the high protein content of cheese, may be involved in these effects. We did not examine the effects of eating other types of milk products in this study, such as goat's milk or plant-based milks like almond milk. Because goat's milk and almond milk contain different amounts of nutrients and fatty acids than cow's milk, drinking these milks would probably have a very different effect on immune cells.

As mentioned earlier, it is not easy to determine if dairy products are healthy or unhealthy. Previous research does not seem to agree on whether eating dairy increases or decreases a person's chance of developing CVD. One reason for these conflicting results may be that dairy products have different nutritional qualities. Conclusions from results of mRNA studies must be made carefully, because these studies can often be complex and the data can be interpreted multiple ways. We also need to see similar results from many different studies, to be confident of our findings. But at this point, our findings suggest that different dairy products may have different effects on our health! In future studies, it is important for researchers to consider categorizing

dairy products into specific groups, rather than considering dairy as one large group.

ORIGINAL SOURCE ARTICLE

Rundblad, A., Holven, K. B., Øyri, L. K. L., Hansson, P., Ivan, I. H., Gjevestad, G. O., et al. 2020. Intake of fermented dairy products induces a less pro-inflammatory postprandial peripheral blood mononuclear cell gene expression response than non-fermented dairy products: a randomized controlled cross-over trial. *Mol. Nutr. Food Res*. 64:2000319. doi: 10.1002/mnfr.202000319

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YOUNG REVIEWERS

AMAYAH, AGE: 16
Amayah is an avid reader. She likes learning new technologies and playing video games.

KAY, AGE: 13
Kay is an avid learner. She likes playing in the band and video games.

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I am a post-doctoral researcher at the University of Oslo. My research aims to find out how our environment, such as what we eat and how much air pollution we are exposed to, affect our health. I am trying to link the exposures from our living environment to our health by looking at e.g., gene expression in immune cells. *amanda.rundblad@medisin.uio.no

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Hi! My name is Patrik Hansson and I am a registered dietitian and associate professor at UiT The Arctic University of Norway and Uppsala University, where I teach students in nutrition and dietetics. The goal with my research is to find out more about how the foods we eat can help us stay healthy, with a special interest in dairy products, fermented foods, and different kinds of fat. My focus is on how these foods can affect blood lipids, cholesterol, inflammation, and gut bacteria.

INGVILD H. IVAN

I have a master's degree in clinical nutrition. In my master's project, I studied the effect of eating different dairy products on inflammation markers. Now, I am working as a registered dietitian.

GYRD O. GJEVESTAD

I worked as a Ph.D., student trying to find out more about how different dairy products, and components of these, could affect health. While working on my Ph.D., I was employed at TINE SA, which is the biggest dairy company in Norway, but I did all my scientific work at the University of Oslo and the Norwegian School of Sport Sciences. After finishing my Ph.D., and changing workplace, I continue to share results from our research together with my former colleagues.

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CAN VITAMINS SLOW DOWN THE BODY'S AGING PROCESS?

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YOUNG REVIEWER:

TIARA

AGE: 10

Some people look younger than their age, others older. Have you ever wondered why? Can we help our bodies age more slowly? Although there seems to be no way to reverse the process of aging, we may be able to slow it down. Improving our diets may help! Humans are born with an internal biological clock within our cells, which reflects the aging state of the body. This is called the epigenetic clock, and it can be changed by what we eat. In this study, we found that women who took supplements of folic acid and vitamin B_{12} had a slower biological aging. More studies on the effects of our diets on the epigenetic clock will help people to live longer and to stay in good health.

EPIGENETICS: TURNING GENES ON AND OFF

The genetic information used to build our bodies and keep them working properly is found in our DNA. That information is organized

in the form of genes. Genes are instructions used to make proteins, which are the building blocks of all our cells. This process of using the information in DNA to make proteins is called **gene expression**. However, cells do not express *all* genes at all times, so our cells need a control system to tell them which genes to express (switch on) and which to switch off. That control system is called **epigenetics** and it is a very complex system.

One of the best understood parts of epigenetics is the process of **DNA methylation**. DNA methylation is performed by a protein called **DNA methyltransferase** (**DNMT**), which adds small chemical units called **methyl groups (CH_3)** to particular places in the DNA sequence (Figure 1). The methylation of the DNA in this way switches genes off. The more spots that are methylated, the more firmly "off" the switch is. Genes involved with maintaining health are increasingly turned off as we age. Turning health-related genes off leads to a greater likelihood of developing diseases as we age.

WHAT FACTORS TURN GENES ON AND OFF?

Although the overall pattern of DNA methylation is similar in most people, the amount of methylation can be increased or decreased by what we eat, by our physical activities, by disease, and by exposure to chemicals or pollutants in the environment. Atmospheric pollution is a concerning problem in many areas of the world and particularly in major cities. This pollution is mostly due to the burning of fossil fuels by factories, power plants, cars, and heaters, and also caused by cigarette smoke. For years, atmospheric pollution has been linked to diseases of the respiratory system, but now that scientists have some understanding of epigenetics, the way these pollutants affect us is better understood. For instance, changes in DNA methylation were identified in diseases related to lung functions in adults exposed to a pollutant called nitrogen dioxide [1]. Also, in children and adolescents,

GENE EXPRESSION

The process by which DNA sequences are read to produce proteins.

EPIGENETICS

The biological mechanism in which gene expression is modified without changing DNA sequences, such as by methylation.

DNA METHYLATION

A biological process in which a methyl group (CH_3), is added to a DNA sequence. Methylation shuts off gene expression.

DNA METHYLTRANSFERASE (DNMT)

A protein capable of DNA methylation.

METHYL GROUP

A small molecule made of one carbon and three hydrogen atoms. It can be added to DNA through a reaction called methylation.

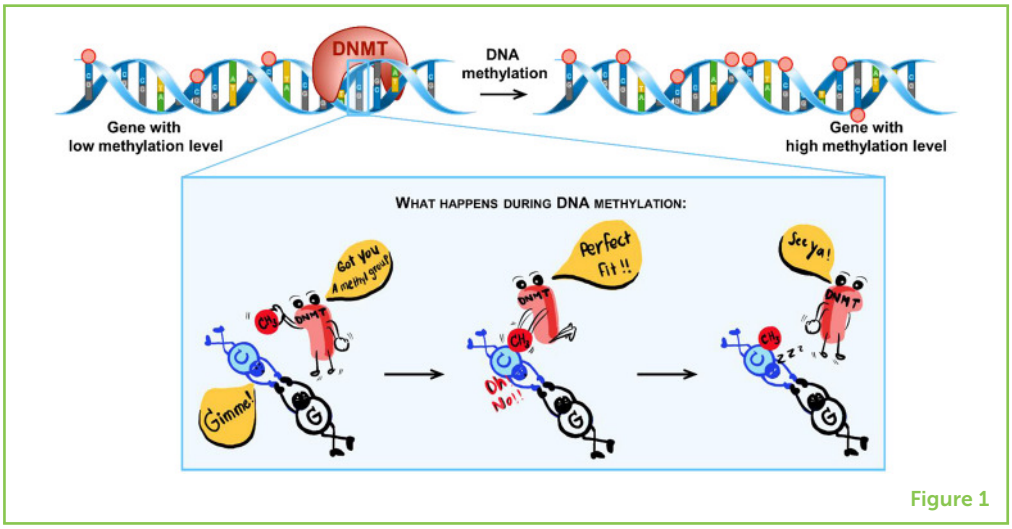

Figure 1

The DNA contained in each cell of the body can be methylated by a molecule called DNA methyltransferase (DNMT). DNMT transfers a chemical group called a methyl group (CH_3), onto the DNA. Methylation of a gene switches it off. The more methyl groups on a gene, the more firmly "off" that gene is.

cases of asthma linked to exposure to atmospheric pollution were associated with changes in methylation levels that could occur *before birth*, showing that pollution can have long-lasting effects on people's health [2].

Fortunately, substances naturally contained in certain foods can combat some of the negative effects of pollution on the body. Several studies have shown that certain vitamins, particularly those of the vitamin B group, can decrease the damage to cells caused by atmospheric pollution. These vitamins act by maintaining a normal level of DNA methylation (Figure 2) [3].

WHAT IS THE EPIGENETIC CLOCK?

BIOLOGICAL AGE

The age corresponding to environment factors like genetics, epigenetics, and lifestyle.

EPIGENETIC CLOCK

A test that calculates a person's biological age using DNA methylation level measurements.

How old are you? This question is easily answered by counting the years since your birth (your chronological age), but what about your **biological age**? Biological age indicates where a person is in their lifespan, based on the damages their cells have sustained. It is interesting that some people look younger than others at the same chronological age, suggesting that factors other than time are at work to cause cells to age. One method researchers have been using to estimate biological age is called the **epigenetic clock** [3]. The epigenetic clock is based on the levels of DNA methylation. As we mentioned earlier, as we age, methylation of our genes, including the genes that keep us healthy and young, increases. So, by measuring DNA methylation at a number of locations on the DNA from several different cells and tissues, and doing some fancy math on those results, scientists can use the epigenetic clock to determine a person's biological age.

Biological age calculated using this method is highly correlated with chronological age [3], which tells us that the epigenetic clock is a good

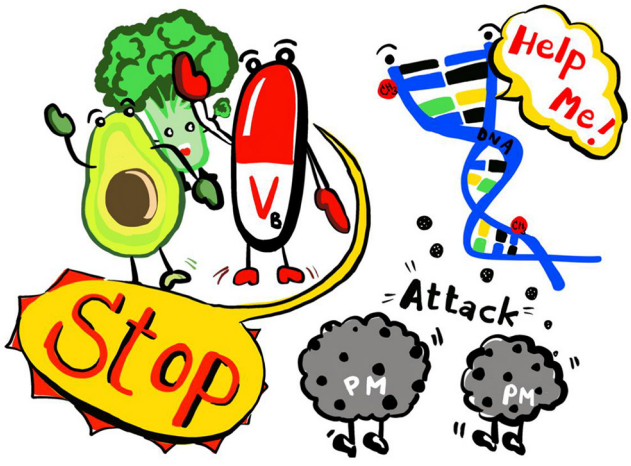

Figure 2

Vitamins can protect DNA against pollution. DNA can be damaged by exposure to pollution, including particulate matter (PM). Pollution can unbalance DNA methylation levels. Methylation changes can cause health problems, but eating a diet rich in beneficial substances like B vitamins can help people stay in good health.

tool for calculating biological age. The epigenetic clock also predicts how quickly diseases like Alzheimer's disease, high blood pressure, diabetes or cancer will get worse. So far, researchers have shown that high-risk lifestyles, like smoking or drinking alcohol, lead to a speeding up of biological aging. On the other hand, a healthy diet can slow down biological aging.

VITAMINS B_9 AND B_{12}

Our bodies need healthy food and a balanced diet to function efficiently. Fruits and vegetables are one of the main food groups containing vitamins. Vitamins are essential for growth, development, and cell function. This means that vitamins help the body to function properly. A long-term lack of a vitamin, which is called a vitamin deficiency, can cause serious symptoms. For example, bleeding gums can result from a lack of vitamin C, and a deficiency in vitamin A causes poor night vision.

B vitamins are important for cell metabolism. Vitamin B_9 is found in dark-green, leafy vegetables such as spinach, broccoli, asparagus and Brussels sprouts. B_9 helps with the synthesis of DNA and RNA, and it is also required for cell division, helping cell growth and development. A deficiency of vitamin B_9 can lead to anemia, which is a problem with blood cell development that leads to poor transport of oxygen and can cause tiredness and weakness. Good sources of vitamin B_{12} are meat, fish, milk, cheese and eggs. Vitamin B_{12} helps to keep blood and nerve cells healthy and also helps to make DNA. Vitamin B_{12} deficiency can also cause anemia. Generally, most people get enough vitamin B_{12} from a balanced diet. However, older adults and people who have a poor ability to absorb vitamins might benefit from vitamin supplementation, which is generally considered to be safe even at high doses.

VITAMINS B_9 AND B_{12} CAN SLOW DOWN THE EPIGENETIC CLOCK

Both vitamins B_9 and B_{12} are involved in biochemical reactions that can increase DNA methylation. However, tiny differences in DNA that naturally exist between individuals, called **single nucleotide polymorphisms** (SNPs) can also play a role in gene methylation. People with a "normal" SNP for the availability of methyl groups have higher methylation levels, but people with a "faulty" SNP in the same location on the DNA have less methylation occurring.

SINGLE NUCLEOTIDE POLYMORPHISM (SNP)

A very small variation in a DNA sequence of an individual.

To understand the impact of B vitamins on biological age, a group of 44 older adults (age 65–75) was studied for 2 years. The diets of study participants were supplemented with vitamins B_9 (400 μg/day) and B_{12} (500 μg/day) for 2 years [4]. To evaluate biological aging, DNA

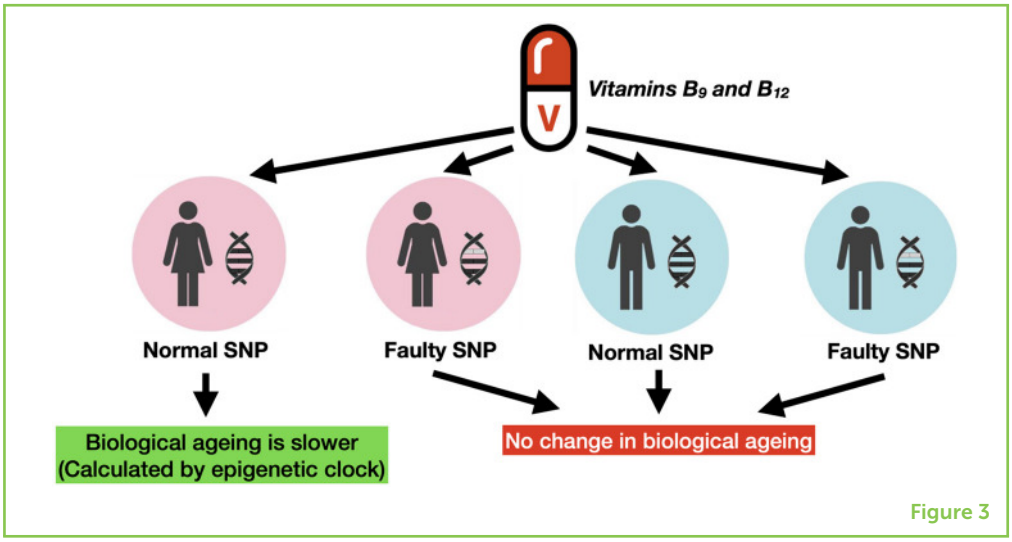

Figure 3

Effects of vitamin B supplementation on biological aging depend on gender and genetics. Following supplementation with vitamins B_9 and B_{12}, female study participants with the normal SNP showed slower biological aging, but females with variant SNP and males did not show a slowdown in biological aging. This means that diet might not affect everyone's epigenetic clock the same way.

methylation levels were analyzed from 353 locations in the DNA, and we put this data into an epigenetic calculator to tell us what their biological age was. In this way, the speed of the epigenetic clock of all participants was generated both before and after supplementation, so that we could compare their real age with their biological age.

Our results showed that, after supplementation, women who carried the normal SNP (the variant that produces a higher methylation activity) had epigenetic clocks that were running slower than those of women with the faulty SNP (Figure 3) [5]. However, the epigenetic clocks of women with the faulty SNP and men were not affected by vitamin supplementation. These results show that the effects of vitamins B_9 and B_{12} appear to be gender and SNP-specific. Although there is no formal evidence for it, the methylation increase observed in women with the normal SNP could have turned off some specific pro-aging genes, with the result of limiting their biological aging over the time of the experiment.

CONCLUSION

Diet plays a role in epigenetic changes, especially in DNA methylation. By looking at the epigenetic clock, we found that vitamins B_9 and B_{12} can slow down biological aging in a gender and SNP-specific manner. Although not everybody is affected by vitamins B_9 and B_{12} supplementation in the same way, our results are encouraging because they mean we might eventually be able to help people to live longer, healthier lives by changing their diets. To achieve this goal, personalized balanced diets could be designed based on the analysis of people's DNA methylation levels. But until we can do this, it is important that we all eat healthy foods, with plenty of vitamins, to keep our epigenetic clocks running properly!

ORIGINAL SOURCE ARTICLE

Sae-Lee, C., Corsi, S., Barrow, T. M., Kuhnle, G. G. C., Bollati, V., Mathers, J. C., et al. 2018. Dietary intervention modifies dna methylation age assessed by the epigenetic clock. *Mol. Nutr. Food Res.* 62:e1800092. doi: 10.1002/mnfr.201800092

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWER

TIARA, AGE: 10

I am a 5th grader. I like to read books and my favorite school subject is library but if that does not count as a subject, I would say reading and if that does not count, then my favorite subject has something to do with reading. My favorite book series is "The Land of Stories" by Chris Colfer. It is a fiction and has everything I like such as fictional dimensions and magic. All the fairy tale characters like Cinderella, Sleeping Beauty, and Rapunzel are in it. My favorite TV show is "Just Add Magic." Soccer is my favorite outdoor play.

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My name is Julien De Biasi and I am a Ph.D. student at the University of Northumbria at Newcastle in the UK. My research work focuses on the analysis of the effects that Maillard reaction products, substances generated in food during heat treatment, can have on the composition and metabolism of the human intestinal microbiota, and how this relates to inflammatory diseases.

JOHN C. MATHERS

John is a professor of human nutrition at Newcastle University in the UK. In addition to teaching students about nutrition and health, he carries out research on nutrition and aging and on the risk of age-related diseases. He was one of the founding members of NuGO—the European Nutrigenomics Organization—that has pioneered the use of modern molecular methods for studying how what we eat affects our health. John is using those methods to investigate links between our eating habits and common diseases, including colorectal cancer.

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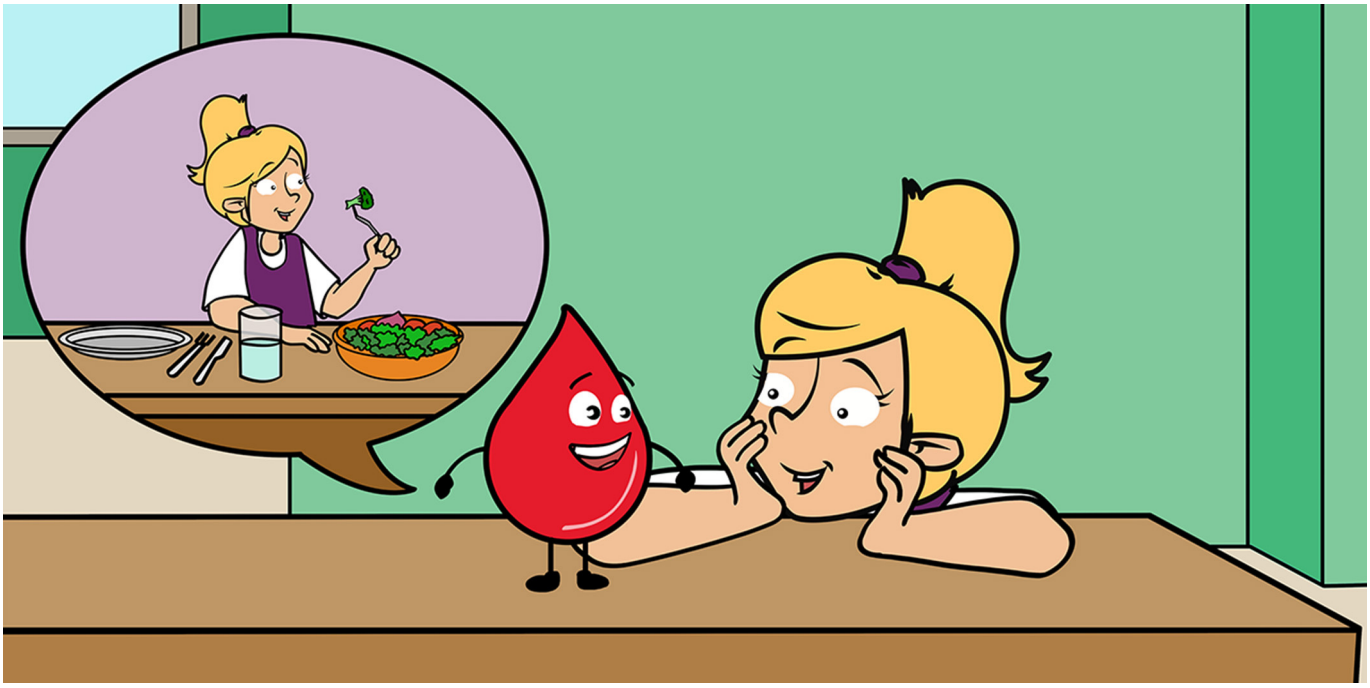

WHAT CAN THE BLOOD TELL US ABOUT FOOD AND HEALTH?

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YOUNG REVIEWER:

JAMIE

AGE: 11

METABOLISM

Chemical processes within the body that keep an organism alive. These processes either use or create energy. Breaking down food into its chemical building blocks is one part of metabolism.

When we eat, foods are broken down into smaller parts by the body. These smaller parts are called metabolites. Depending on the foods we eat, different metabolites enter the body. Microbes living in the gut can also take part in making metabolites. Metabolites from food or microbes can both appear in the blood. Studying blood metabolites could tell us what kinds of foods people generally eat or how healthy they are. To find out how eating different foods changes blood metabolites, we collected results from many previous experiments. We found that studying blood metabolites can tell us how food affects people's bodies. Interestingly, we also found that these effects appear to be different for each person.

INTRODUCTION

The chemical processes that happen in our bodies to keep us alive are collectively called **metabolism**. The fuel for these processes primarily

comes from the foods we eat. After food enters the mouth, many things happen. In the mouth, food is chewed up into a paste-like form; then, it travels through the digestive system. As it travels along, the food is broken down into small pieces, called **metabolites**. When the metabolites arrive in the small intestine, which is toward the end of the digestive tract, they are transported into the blood. The blood delivers the metabolites to the rest of the body and its organs. The leftover food that we cannot break down then reaches the large intestine, which is the home to many gut **microbes**. The community of gut microbes, which is called the **gut microbiota**, helps us to break down the leftover food into smaller pieces. They eat a bit, but they return the rest to us. We can absorb some of the metabolites created by the gut microbes. We get rid of the leftover food that we do not need when we go to the toilet (Figure 1).

Because one important mission of the blood is to feed the rest of the body, the blood contains a lot of metabolites. These metabolites come directly from food or are created as food is processed through the digestive system. If we measure metabolites in people's blood after they eat specific foods, these measurements can give us information about how healthy the people are or which foods they ate. We can also get information about the gut microbiota, including which organisms live in the gut and how they change the metabolites.

METABOLITES

Chemical building block of food. Metabolites can be produced by the body or the gut microorganisms, and they can be converted from one form to another.

MICROBES

Tiny microorganisms, like bacteria, viruses and some fungi, that cannot be seen with the naked eye.

GUT MICROBIOTA

The total community of microorganisms (microbes) living in the gut.

WE ARE ALL UNIQUE, INCLUDING THE WAY WE DIGEST FOOD!

We are all unique. We have different colors of skin, eyes, and hair. Some of us play soccer, some dance ballet. Boys and girls are also different.

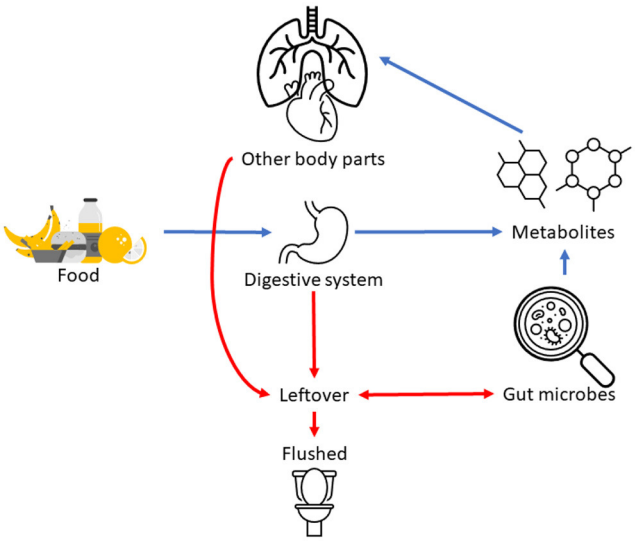

Figure 1

Metabolites from food are broken down by the digestive system and transported to other body parts. In the intestines, leftovers are eaten by gut microbes, and the remainder of the waste is flushed down the toilet. Blue arrows show the flow of metabolites and red arrows show the flow of the leftovers.

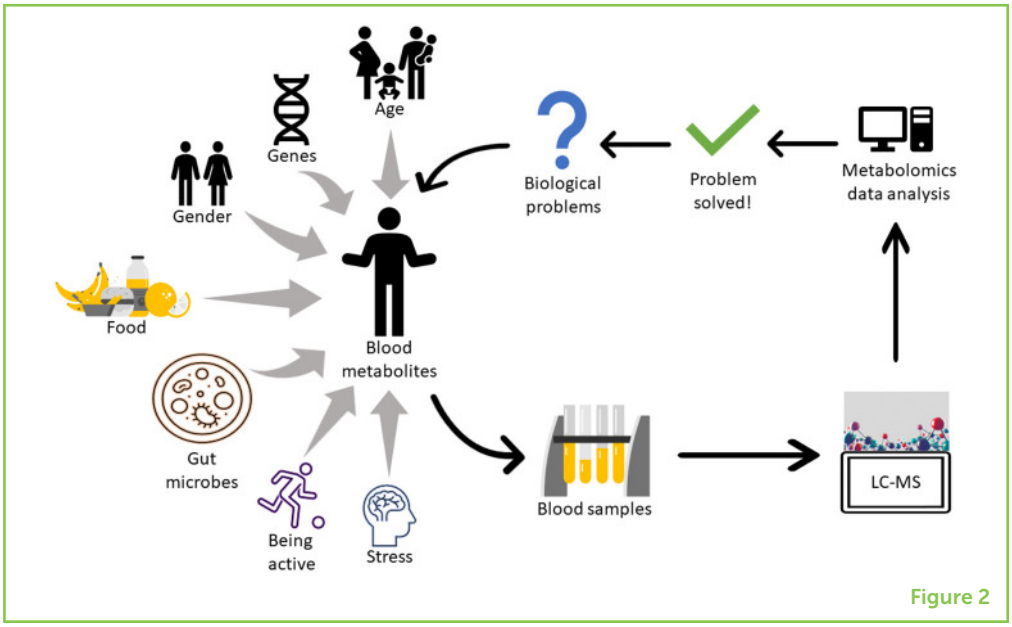

Figure 2

Figure 2

Metabolomics can be used to answer questions about what people eat and how the body manages metabolites. Many varied factors, shown on the left, affect how our bodies manage metabolites from the foods we eat. LC-MS is the scientific technique used to detect metabolites in blood samples. Metabolomics can help us answer many biological questions and can teach us about how every person's metabolism is unique.

Since we are so different on the outside, can we also assume that we have different processes inside our bodies?

We all eat different foods. Even within the same family, family members may have different favorite pizzas or soups. Maybe you like to eat chocolate or cakes, but your parents or grandparents may not enjoy those sweets as much anymore. They might not run and jump as much as you do, either! Different foods contain different types of metabolites. Therefore, when we eat different foods, we introduce many different metabolites into our bodies.

As we mentioned, the gut contains many microbes. Since the foods we eat vary a lot, the gut microbiota also varies a lot from one person to another. Your microbes are unique to you, just like your fingerprints. Your parents or siblings may have a similar set of microbes, but their gut microbiota will not look exactly the same as yours, even if you have a twin sibling [1]. Your unique set of gut microbes processes food uniquely within your gut.

If two people make cookies using different ingredients, methods, and toppings, they will end up baking different cookies. Similarly, because you are different from other people in how you look, your weight, your age, the foods you eat, the microbes in your gut, and how much exercise you get, the way you process your food may also be unique! Therefore, you and your siblings may have different chemical reactions going on in your bodies, even when you eat exactly the same foods [2]. Moreover, there are things we cannot see, like stress, that also cause differences in the way the body works. Since all these things affect how metabolites are created, you also have a unique set of metabolites (Figure 2)!

HOW DO WE STUDY METABOLITES?

What if we could check the metabolites inside each person? We would get information on how these metabolites differ from one person to another. Further, this information could give us some hints about the foods people eat, how their microbes act, and how their bodies process food. Well, we *can* do this!

First, we must take a small sample from the body. Depending on what we want to know, we can use samples of blood, urine, poo, or even exhaled air. We will focus on the blood because it carries the metabolites from the digestive system to feed the whole body. The blood sample is processed in the lab so that only the metabolites are left, in a clear liquid. This liquid can then be studied using a technique called **metabolomics**.

METABOLOMICS

A technique to get information about many metabolites from a sample of blood or other bodily fluid or tissue.

LC-MS

A machine called liquid chromatography-mass spectrometry that helps us to study metabolites present in a sample.

Metabolomics gives us information about the metabolites in a sample. Metabolomics uses a technique called **liquid chromatography–mass spectrometry** (**LC-MS**), which separates the metabolites from each other and shows how many metabolites are in each sample. Metabolomics analysis can give us a lot of information—it can tell us about hundreds or thousands of metabolites at the same time. We can then use this information to answer our research questions (Figure 2).

HOW DOES FOOD AFFECT OUR METABOLITES?

We wanted to know whether metabolomics studies of blood samples could tell us about how unique each person's metabolism is. We looked for past metabolomics experiments done by other researchers, to help us understand what has already been discovered and what we need to do next. We found 49 experiments reported in the last decade that studied levels of blood metabolites after various foods were eaten [3]. We grouped the studies based on how the metabolites are made, for example, whether they are produced by the body or by the gut microbiota. We were curious to see if the same groups of metabolites were generated by eating the same foods, or if one type of food consistently affected the same group of metabolites. We also wanted to see if metabolites were different between different groups of people. By examining these past studies, we learned at least three lessons.

First, different foods can affect our bodies differently. Though we may not realize it, food is complicated. How much oil we eat, whether we eat soy or dairy, or whether we eat more or less than usual activates different reactions in the body. As an example, having lots of dairy milk with breakfast increases different metabolites in the blood compared to a breakfast containing soy milk [4]. However, these results also depend on the people themselves. For example, people who were

heavier seemed to show different reactions than people who were underweight [5].

Second, different types of metabolites can be affected by the same food. Let us take fish as an example. Fish is rich in protein. However, eating fish not only increases amino acids, the building blocks of protein, but also increase certain sugars in the body [6]. Also, similar metabolites can be affected by different foods. For example, the same metabolites changed after people ate soy, milk, meat, or whole grains, even though these foods are quite different from each other [6–8].

Lastly, the work of the gut microbiota plays an important role. In the experiments we compiled, almost all the foods investigated changed the metabolites produced by gut microbes. Some metabolites seemed to be found more often in healthy people than in people who were not well. On the other hand, other metabolites were found only in people with certain illnesses. We do not know yet if having a particular gut microbiota makes a person healthier or if the opposite is true—if healthy people tend to grow a different gut microbiota than people who are unwell. We need to do further research to figure this out.

CONCLUSION

Metabolomics can provide researchers with information about blood metabolites. These metabolites can tell us many things because they are affected by our body shape, age, and what we eat. Metabolites can also tell us about other processes happening in the body, like what the gut microbes are doing. By studying what other researchers have done, we learned that similar metabolites can be affected by different foods. Conversely, different groups of metabolites can be affected by the same foods. Based on these lessons, we think that, in the future, metabolomics could be used to find out how the foods we eat are related to health. This information could help us to better understand how and why people react differently to the same foods. Since we still do not know what causes these differences, further research is needed. Hopefully someday we will be able to use metabolomics to find which combinations of foods work best for each individual, so that we can all choose foods that help our unique metabolisms to work properly and keep us healthy.

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YOUNG REVIEWER

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I love playing piano and drawing. My favorite sports are football and badminton. I love to hang out with my friends and family. I like to explore new things.

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I am professor at the research area "Food and Health" that I approach from the view of nutrition at the Institute of Public Health and Clinical Nutrition, University of Eastern Finland. My research interest is in the health effects of diets, foods, and food components with special focus on gut-mediated effects, such as digestion, inflammation, and microbiome interaction. In my free time I enjoy trailrunning with

my dogs, skiing in winter, and spending time at our summer cottage at the lake with its doings.

KATI HANHINEVA

I am professor at Food Chemistry and Food Development unit at University of Turku. I completed Ph.D., in biotechnology at the University of Kuopio 2008. Since 2014 I have been the principal investigator in food and nutritional metabolomics research group, where we have focused on studying why and how different foods have different effects on our body and health. A special focus in our research is on the role of the small bugs in our intestine, the gut microbiota, and the favorite tool in our studies is the metabolomics analysis.

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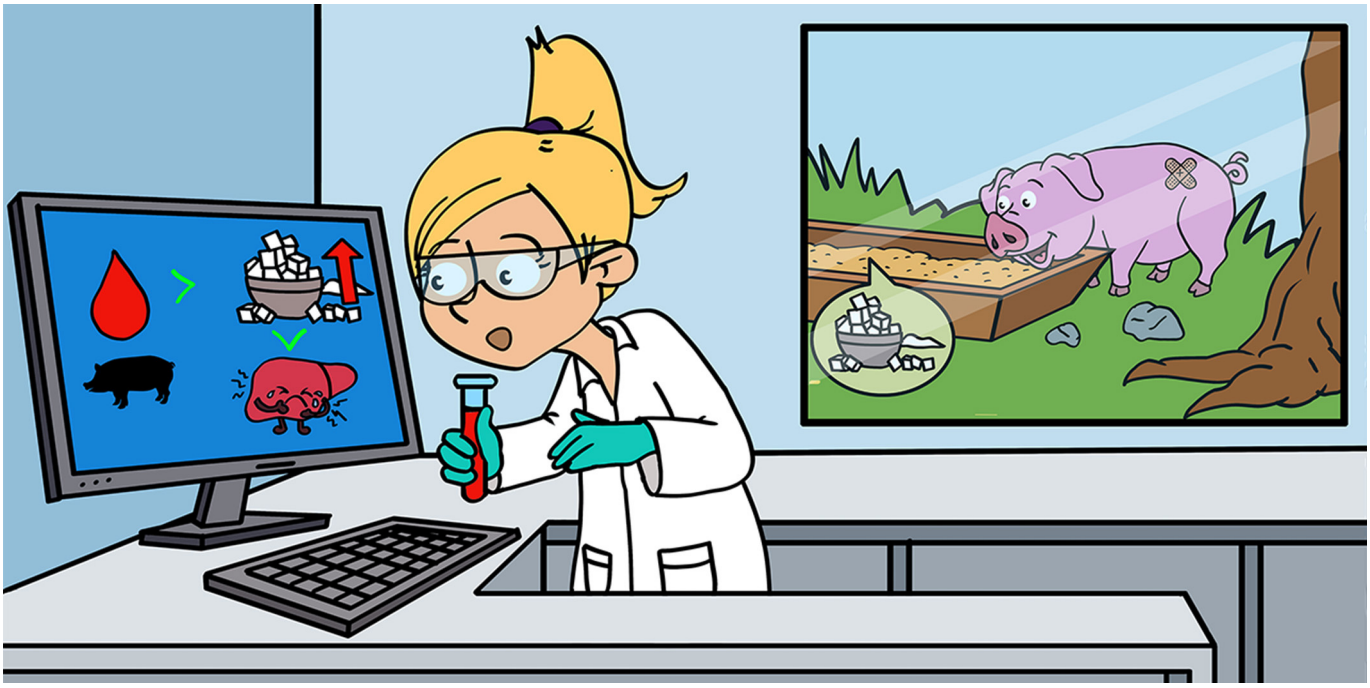

HOW DOES YOUR BODY DEAL WITH FAST-FOOD MEALS?

Nathalie Poupin [1] ***and Sergio Polakof*** [2*]

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YOUNG REVIEWER:

YOONSA
AGE: 13

Eating a less-than-healthy diet can increase the chances of becoming obese, which usually happens when body organs have difficulties using or storing the excess fat and sugar that we eat. To better understand how what we eat affects the functioning of our organs, we measured substances called metabolites, which come from food, in the blood of obese minipigs. We then used computers to figure out what happens to these metabolites inside the liver following normal meals or a fast-food meal. We found that the liver fights against unhealthy food by finding ways to use or remove the excess fat and sugar. However, some of the paths normally followed by healthy food might become blocked when we eat too much unhealthy food. Our work showed that a better understanding of how the liver processes the metabolites from unhealthy diets could help people suffering from the effects of obesity.

WHAT IS OBESITY?

The fat that we eat is stored in a specific type of tissue called **adipose tissue**. Adipose tissue is made of cells called **adipocytes**, or fat cells. Stored fat comes from the fatty foods we eat, but it also comes from sugary foods because the body can convert sugar to fat. **Obesity** is a chronic disease, in which too much fat is stored in the adipocytes, making them grow bigger and causing the body to become fatter. Obesity eventually leads to more serious health problems, like **diabetes**. When too much fat or sugar is consumed, it is stored in the adipocytes, but it can also be stored in the liver. The liver is a very important organ because it is in charge of handling sugar and fat. Since the main role of the liver is not to store fat, too much fat can be toxic for this organ, making it difficult for it to work normally. This can be very dangerous for our health. Therefore, it is important to understand how the liver uses the fat and sugar we eat, especially when we consume too much junk food or too many fast-food meals.

WHAT IS METABOLISM?

All organs are fed by blood vessels, which bring them the molecules they need to function properly. These small molecules are called **metabolites**. Metabolites that are transported by the blood to the organs can come from the foods we eat, or they can be made by other organs. Organs use metabolites to make energy, or as building blocks to create other bigger molecules that the organs need to function. Organs can also make new metabolites and send them back to the blood, so other organs can use them. The transformations of metabolites into other metabolites are called metabolic reactions. A chain of metabolic reactions first forms a metabolic pathway, and then all these pathways form a huge "road map," called a **metabolic network** (Figure 1).

The metabolic network of an organ can be compared to the road map of a city. In a city, some goods are produced in factories and then transported to shops where they can be stored and later delivered to your house. When everything works well, the shops are continuously supplied by the factories and goods can be delivered to your house whenever you need them. When a road becomes blocked by an accident or by too much traffic, there may be some delays in the delivery. Everything gets really messy when too many roads become blocked: shops might become empty and unable to deliver the goods you need. The same might happen to the metabolic network when a person becomes fat or obese: some metabolic pathways might be blocked, causing the organs struggle to do their normal work, either not making metabolites that need to be made or storing large amounts of metabolites that should be sent to other parts of the body.

ADIPOSE TISSUE

Parts of our body which are composed mainly of adipocytes and which store fat.

ADIPOCYTES

Cells whose main function is storing fat. They are also called fat cells.

OBESITY

A disease which starts developing when too much fat is ingested and needs to be stored in the body.

DIABETES

A condition that occurs when the body can't use sugar normally. Too much high sugar levels will eventually lead to long-term damages in multiple organs.

METABOLITES

Small molecules that are directly ingested from foods or produced in the body by transforming other molecules or breaking down bigger molecules.

METABOLIC NETWORK

The complex web of relationships between metabolites, composed of many interlinked metabolic pathways.

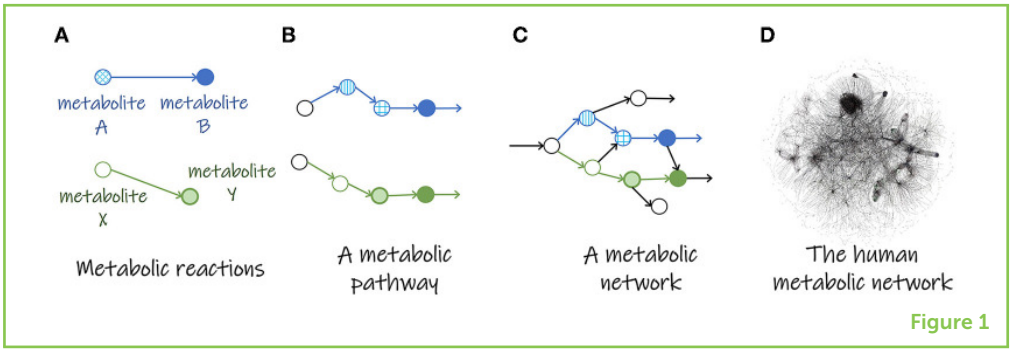

Figure 1

The metabolic network. **(A)** In metabolic reactions, metabolites (A or X, represented by circles) are transformed into other metabolites (B or Y), as shown by the arrows. **(B)** A chain of metabolic reaction forms a metabolic pathway. **(C)** A metabolic network is a combination of many metabolic pathways. **(D)** The human metabolic network illustrated here contains 13097 reactions and 10067 metabolites. (Image credit: [1], using the MetExplore webserver [2]).

In our study, we wanted to understand which paths of the liver's metabolic network are blocked or disturbed in obese people and how this might affect their health.

STUDYING THE EFFECTS OF OBESITY ON ORGANS

To understand how our organs deal with the fat and sugar we eat, we must use a living animal as a model. If the animal model is similar enough to the human, it can help us understand what happens in the human body. Rats and mice are the most commonly used animal models, but in our study we chose to use the minipig. The minipig is very similar to a common pig but smaller, even as an adult. Minipig organs work very similarly to human organs and minipigs also digest food in a similar way. Minipigs eat several meals each day, like humans do. Because minipigs are bigger than rats and mice, we can obtain bigger blood samples from them and take blood more often. Finally, minipigs are a very good model to study obesity because they show the same symptoms as humans [3]. To study what happens in minipigs' organs when they become obese, we fed minipigs meals containing a lot of fat and sugar (like fast-food meals) every day for 2 months. We weighed the minipigs every week. After 2 months, we took blood samples to measure the amounts of sugar and other metabolites in the minipigs' blood.

COMPUTER MODELS CAN HELP US UNDERSTAND WHAT HAPPENS IN OUR ORGANS

To understand how an organ works, we often need to take samples from it—but this can be complicated. Instead, we took blood from the vessels that enter and leave the liver of minipigs, to study which metabolites, and how much of them, are present in the vessels. In the laboratory, hundreds of metabolites can be measured at once using a technique called **metabolomics** [4]. By comparing the amount of each metabolite at the entrance and exit of the liver, we can see which metabolites have been produced or used by the liver. This tells us about what is happening inside that organ (Figure 2). Then we can compare what happens in the liver under various conditions. For example, if we observe that the amount of glucose (a sugar metabolite that is

METABOLOMICS

Laboratory techniques that help to identify and measure the amounts of thousands of metabolites that are present in a sample of blood or body fluid or organ.

Figure 2

Understanding liver metabolism using metabolomics and computer modeling. Blood is taken from the vessels entering and leaving the liver. Metabolomics is used to see which metabolites (such as glucose and pyruvate) are present and in what quantities. We use computer modeling to figure out if the metabolites were produced or consumed by the liver (1). For example, if we measure more glucose in the outgoing vessel than in the incoming vessel, it means that glucose is produced by the liver. The computer model helps us learn about what happens inside the liver and the paths followed by various metabolites (2).

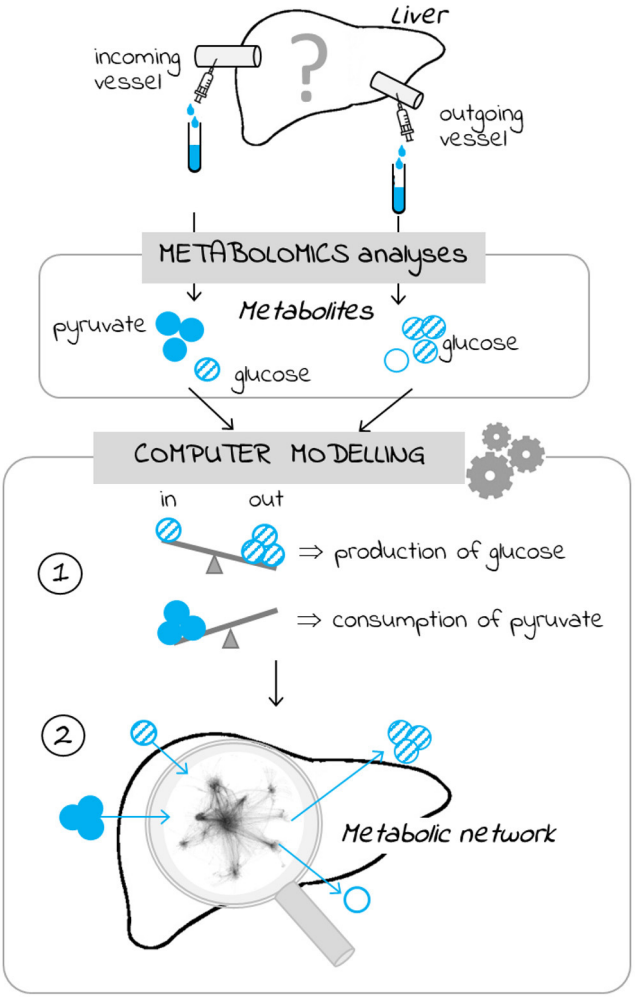

Figure 2

the main fuel for cells) coming out of the liver is much lower in one condition than in another, it may mean that less glucose was produced in that condition. Maybe the road producing glucose was blocked, or the glucose was used to make something else (Figure 3).

This kind of reasoning is easy to do for one metabolite. However, when you have *hundreds* of metabolites and many roads, it is too difficult for the human brain to figure out which metabolic roads are blocked. Fortunately, computers can help! In this case, the **computer model** is like a GPS or Google Maps: using calculations and some information about the traffic, it can help scientists figure out which roads are blocked, and which are not. In our case, computer models helped us to guess which metabolic roads were used by the metabolites, giving us new ideas about what may be happening in the liver. We could then check these ideas using other experiments.

COMPUTER MODEL

A computer program that uses mathematical calculations and rules to reproduce the functioning of an organ (like the liver, in our case) and predict how things will behave under different conditions.

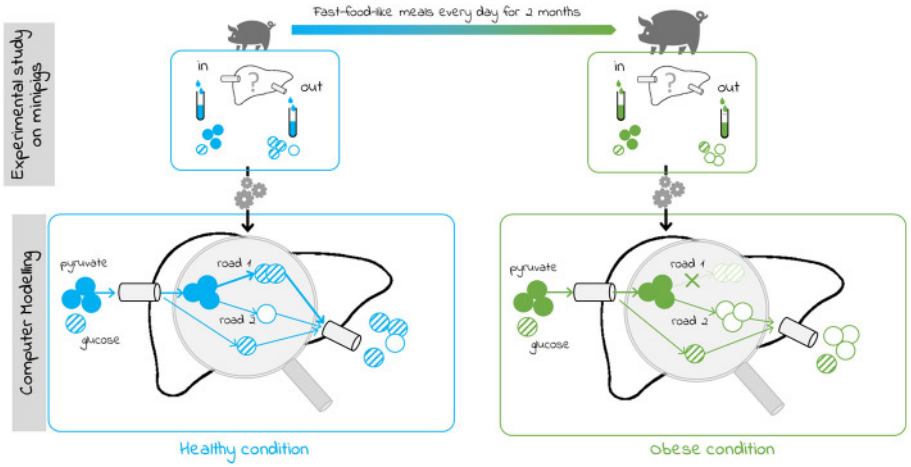

Figure 3

Figure 3

What is happening in the liver of obese minipigs? Our model can help to understand what happens in the liver. It searches paths that were followed by the metabolites present in the incoming vessel to obtain the metabolites present in outgoing vessels. For example, in the "healthy" condition, glucose but not pyruvate was present in the outgoing vessel, meaning that glucose was produced by the liver and pyruvate was used up. The model proposes that path 1 was used. In the "obese" condition, less glucose was present in the outgoing vessel t: the model predicts that path 2 was used instead of path 1 because path 1 might be blocked.

OBESITY CHANGES THE WAY OUR ORGANS DEAL WITH FOOD

After only 2 months of eating fast-food-like meals, the minipigs became obese. They stored large quantities of fat in their bodies and we also found larger amounts of sugar in their blood. Thanks to metabolomics, we identified which metabolites, and how much of them, were present at the entry and exit to the liver. With the help of computer models, we learned that, after eating fast-food for 2 months, the minipigs' liver did not work as well as they usually did in the healthy condition.

What went wrong inside the liver? The liver of obese animals changed the way they used or produced metabolites. Also, the metabolites did not take the same "roads" inside the liver when the minipigs were obese. Using the new roads had negative consequences for the obese minipigs: their liver stored more fat and became less able to deal with fast-food meals. The liver is very important for controlling the amount of fat and sugar in the body. Therefore, if the liver does not work correctly and starts to store too much fat and sugar, it can lead to serious health complications, like diabetes. We found that, even after just 2 months of eating fast-food meals every day, the consequences for the liver were already very negative.

CONCLUSIONS

The liver is one of the most important organs in the body: it is the primary organ that tries to protect us from the bad consequences of unhealthy food. In obese minipigs, thanks to metabolomics and computer models, we figured out that when too many fast-food meals are eaten, the liver starts to use the metabolites incorrectly. These changes may push the liver to store more sugars and fats in an attempt to protect the body. Too much fat and sugar stored in the liver can have

harmful consequences for other organs and disturb the way the whole body deals with fat and sugar. These changes could be the beginning of serious diseases, like diabetes. If the human liver works like the minipig's liver, we believe that these negative consequences could also happen in humans who eat too much fast-food. This evidence supports the idea that a balanced diet, low in fat and sugar and high in fruits and vegetables, could help to keep the liver, and therefore the entire person, healthy.

ORIGINAL SOURCE ARTICLES

Tremblay-Franco, M., Poupin, N., Amiel, A., Canlet, C., Rémond, D., Debrauwer, L., et al. 2020. Postprandial NMR-based metabolic exchanges reflect impaired phenotypic flexibility across splanchnic organs in the obese Yucatan mini-pig. *Nutrients* 12:2442. doi: 10.3390/nu12082442

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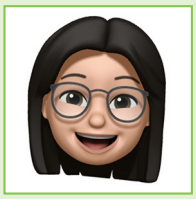
YOUNG REVIEWER



YOONSA, AGE: 13

My name is Yoonsa and I am 13 years old. I play the violin and piano, and recently started to learn the viola. I am interested in marine biology, and when I was younger, I wanted to become a marine mammal vet. In my free time, I like to read, sight read ("zilch") chamber music with my friends, and play with my mini schnauzer.

AUTHORS

NATHALIE POUPIN

I am a young researcher particularly interested in understanding the functioning of cells and tissues and how they are affected by specific conditions, like food contaminants. I am a bioinformatician, which means that I use the results of experiments performed by biologists to construct computer models of the cells and tissues. I use these models to simulate what might happen in the real world. I particularly enjoy collaborating with scientists from different fields and sharing knowledge and ideas. Outside of work, I really like outdoor activities such as biking, running and gardening.

SERGIO POLAKOF

Since I was a child, I have always been interested in understanding how the bodies of animals and humans work. That is what a physiologist does: figures out how the body responds to the environment. I think that the ways our bodies adapt to our diets to stay in good shape and avoid chronic diseases is fascinating. By better understanding how this happens, I believe that we can protect ourselves from some chronic diseases through proper nutrition. Observing and taking care of nature is still my major hobby today, so I really enjoy running, hiking, and biking in the mountains and the woods. *sergio.polakof@inrae.fr

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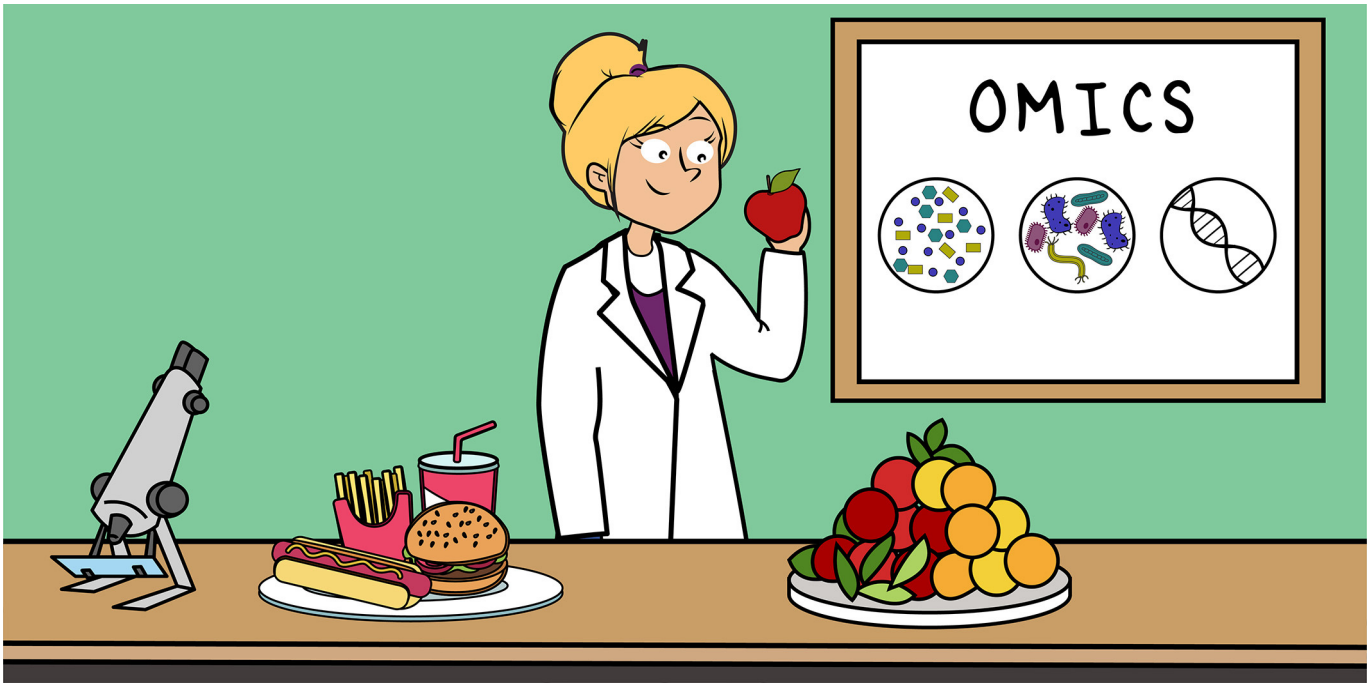

HOW CAN NEW PERSONALIZED NUTRITION TOOLS IMPROVE HEALTH?

***Katherine J. Li*[1,2*], *Kathryn J. Burton-Pimentel*[2], *Elske M. Brouwer-Brolsma*[1], *Guy Vergères*[2] and *Edith J. M. Feskens*[1]**

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YOUNG REVIEWERS:


ABHAY
AGE: 10


ELLE
AGE: 12


JOSI
AGE: 9


KAVISH
AGE: 9

All living creatures need to eat. Eating a variety of different healthy foods in moderate amounts is important. How do we know which foods are healthy? Researchers can compare the foods consumed by healthy and unhealthy people by asking what and how much they eat. Unfortunately, people cannot always remember what and how much they eat, which makes it difficult to figure out which foods are healthy. Recently, researchers discovered that a group of research tools called omics could help. When people eat, the building blocks of food are broken down into small compounds called metabolites. With laboratory equipment, researchers can measures these metabolites in food and in the body, to help them get a better idea of which foods are healthy or unhealthy. Researchers can also use omics tools to find the best foods for each unique person so that we can all stay healthy and happy.

MEASURING WHAT WE EAT

Food gives us the energy to move, and nutrients to help us grow. Nowadays, many people are interested in what they should eat to prevent disease and live long and healthy lives. But how do we know which foods are healthy? To tell people what they can eat to stay healthy, researchers must first understand what healthy and unhealthy people eat. Currently, we do this by asking people questions about what they eat, how much, and how often they eat various foods. We could ask them what they ate yesterday, or what they normally eat. We can also ask people to write down exactly what they eat, like a food diary. To find out about what people normally eat, we often use a questionnaire with questions like, "How many times do you eat fish in a month?" Collecting information about foods in a person's diet over a certain period of time is called a dietary assessment [1]. Researchers link this information with food composition tables (which contain information about the types and amounts of nutrients inside a particular food, including carbohydrates, protein, fat, fiber, sugars, salt, vitamins, and minerals) to calculate the amount of energy and nutrients that person gets from his or her diet.

INVESTIGATING THE LINK BETWEEN FOOD AND HEALTH

NUTRITIONAL EPIDEMIOLOGY

A field of research that studies the relationships between a nutrient, food, or diet and the health of a large population of people.

After figuring out what and how much people eat, researchers who study **nutritional epidemiology** want to know if diet (or a certain food or nutrient in the diet) influences the chances of people getting sick. These researchers are like detectives: they ask the right questions to gather the evidence (data), and they use it to figure out if a food is linked to a crime scene (the disease) (Figure 1). Imagine that you are a researcher given the task of figuring out whether eating fish can help prevent heart attacks. What would you do? First, you might want to gather information from many people, asking them if they eat fish and how often (dietary assessment). Second, you would need to find out whether those people have had heart attacks (health assessment). You may also want to collect information on each person's age, sex, and job, as this information could give you clues about the people's health or which foods they tend to choose. You could also collect blood samples to measure early signs of a heart attack, like blood cholesterol levels. Then, you could analyze the data using math to see if there are differences in the health of people who eat a lot of fish and people who eat very little fish. If you do this, you are doing an observational study. Researchers in nutritional epidemiology look at data collected from lots of observational studies to make links between foods and health. The government can then use this information as evidence to help create dietary guidelines, which are a set of recommendations for the public on what they should eat if they want to be healthy.

Figure 1

How researchers in nutritional epidemiology investigate links between food and health.

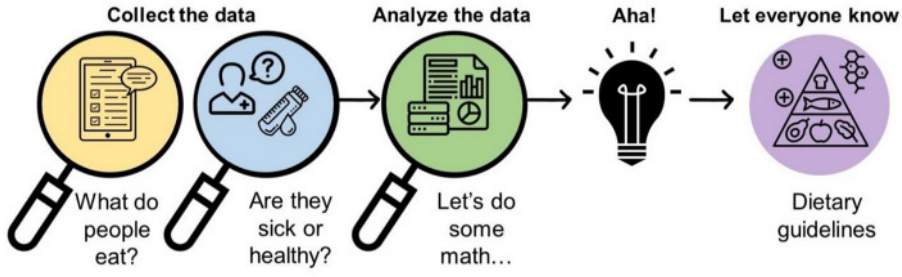

Figure 1

MISTAKES AND MISSING INFORMATION LEAD TO CONFUSING EVIDENCE

This may sound like a straightforward path: collect information on what people eat and their health, see if there is a link between what people eat and whether they get a certain disease, and use this information to advise people on what to eat. But unfortunately, it is not so simple. Often the evidence researchers find does not seem to fit together very well, and it is difficult for researchers and the government to decide which type of diet to advise. One reason for this difficulty is that the dietary assessment used in these studies relies on people telling researchers what they ate, which is not always a good strategy. Can you remember *exactly* what you ate yesterday? How about last month? Sometimes, people simply forget what they ate. Estimating *how much* they eat can be even more difficult, because different people might have different ideas about what portion sizes of various foods should be. Your idea of one piece of fish may be much larger or smaller than someone else's! Other times, people may lie about eating certain foods because they feel embarrassed about what they ate. We often underestimate how often we eat junk foods and overestimate how often we eat healthier foods like fruits and vegetables. In all these situations, scientists' dietary data already contain a lot of mistakes, even before these data are linked to disease data.

Another reason for the confusing evidence about which foods to eat is that researchers actually know very little about what is inside of foods. Each food is made up of many different compounds that are like the building blocks of the food (Figure 2). When we digest food, some of these building blocks are further broken apart into small compounds called **metabolites**. Currently, food composition tables contain information on about 150 compounds that are important nutrients in the human diet, including carbohydrates, protein, fat, fiber, sugars, salt, vitamins, and minerals [2]. But there are over 26,000 compounds found in foods, and this number is still growing! Researchers also do not know very much about the many metabolites that are generated from the compounds in foods once they are eaten.

METABOLITES

Small compounds that are produced when the body breaks down foods or larger compounds in the body. Some metabolites are necessary to provide energy, or to maintain health.

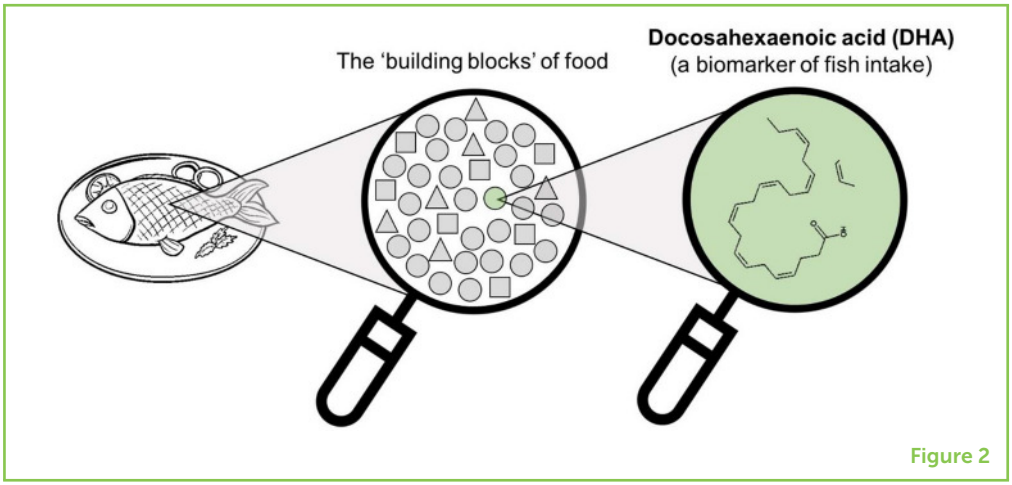

Figure 2

Foods are the source of thousands of compounds and metabolites (the building blocks), each of which can have a different role on human health. Some compounds can act as biomarkers of food intake, which are signals that researchers can measure in the body that can tell them more about what which foods people ate. Docosahexaenoic acid (DHA) is a biomarker for fish intake.

Each of these compounds and their metabolites can have its own effects on human health.

NEW TOOLS THAT CAN IMPROVE OUR UNDERSTANDING OF BOTH FOODS AND HEALTH

Recently, researchers have discovered some new ways to uncover more clues about how foods affect health. As a group, these are called omics tools (Figure 3A). One of these tools is called **metabolomics**. Using laboratory equipment, researchers can measures thousands of metabolites from a food at once! Metabolomics can help us to get a better idea of which foods are healthy or unhealthy. Researchers can also use metabolomics to measure metabolites in the human body, such as in the blood, urine, hair, or even toenails! Some of these metabolites can act as **biomarkers**, which is short for biological markers. Biomarkers are signals in the body that can help researchers understand both food intake and disease. Biomarkers of food intake can be used to help confirm what people ate, and correct mistakes in dietary assessment in our observational studies [1]. Docosapentaenoic acid (DHA) is an example of a food biomarker (Figure 2). It can be found in the fat tissues of people who eat fish [3].

METABOLOMICS

An area of study that measures all of the small molecules (metabolites) in our foods and in our body.

BIOMARKER

A signal that researchers can measure in the blood or other body fluid or tissue that can tell them more about which foods people ate, and if people's bodies are working well.

BUT IT IS COMPLICATED

Sometimes, two people could eat the same things, but one person could be healthier than the other. How can this be? Since we are all unique, each person can have a different health response to the same foods. This is partly influenced by a person's individual genes. Another tool called **nutrigenomics** can help researchers better understand how diet influences which genes are turned on or off, and also how genes can affect the way a person's body reacts to foods and nutrients. Foods and genes are constantly playing a poking game—foods that "poke" a person's genes can change which genes are turned on or off

NUTRIGENOMICS

An area of study that analyzes the relationships between genes, diet, and health.

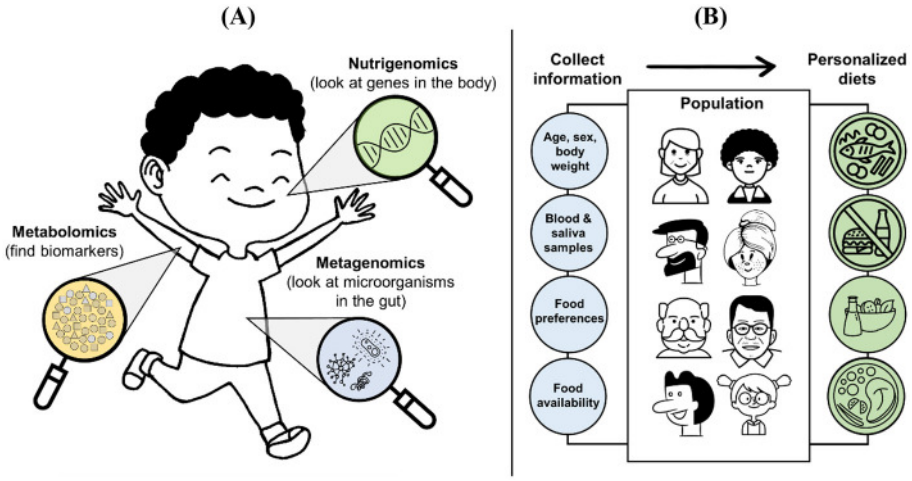

Figure 3

(A) New omics tools in food and nutrition research help researchers to understand how genes and diet influence each other, how the gut microbiota can impact health, and which biomarkers can help measure food intake more accurately. **(B)** To introduce personalized nutrition to a population, researchers must first collect information from them, including age, sex, and body weight, as well as information on which foods they prefer and which foods are available. Researchers could also measure biomarkers from blood samples and collect genetic data from saliva samples. This information can be used to help personalize people's diets.

GUT MICROBIOTA

The entire community of microorganisms (including bacteria) that live in the gut.

METAGENOMICS

An area of study that analyzes all of the genes of the microorganisms from a (bio)sample. Metagenomics can be used to analyze the gut microbiota from a fecal sample.

PERSONALIZED NUTRITION

A field of research that aims to find the best diet for each unique person, to keep that person healthy or help him or her prevent, manage, and treat disease.

and impact health, while genes can "poke" back to influence the body's response to a food.

Different people also have different microorganisms living in their bodies. After food is chewed and swallowed, it travels down the digestive tract to the gut. There, the food is greeted by *millions* of microorganisms that can help to further break down the food. The whole community of microorganisms in the gut is called the **gut microbiota**. Each person has a unique gut microbiota. Researchers can measure the microbiota (and their genes) using a new tool called **metagenomics**. Since these microbes break down foods, they can also produce metabolites, which can affect health. The gut microbiota can even affect a person's risk of getting diseases such as a heart attack [4].

Every person is unique. Our uniqueness is why dietary recommendations for the public sometimes do not work for everybody. By using omics tools in research, researchers can find out how people respond differently to the foods they eat. Then, we can help individuals or groups of people who are at risk for certain diseases, such as heart attacks, by offering them **personalized nutrition** advice (Figure 3B) [5].

THE FUTURE OF FOOD AND HEALTH IS PERSONALIZED!

It is an exciting time for researchers! We have always known that the human body is unique and complex, and that finding the link between food and health is not simple task. But with new omics tools, we are starting to learn more about the role of various food components, as well as genes, microbiota, and metabolites, for preventing certain diseases. We still have a lot of work to do, especially in regards to how diets should be personalized and making sure that personalized

nutrition is available to everyone, but there is a lot of promise. Imagine going into a grocery store in the future, where you can choose foods off the shelves based on your age, body weight, and maybe even your genes or gut microbiota—how cool would that be? The challenge in the future may be finding the right balance, so that we can eat the foods our bodies need to eat to stay healthy, but still have the joy of sharing a meal with our friends and family.

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ABHAY, AGE: 10

I am a fourth-grader who loves movies and reading. I am a big fan of movie franchises such as Marvel and Star Wars and book collections such as Geronimo Stilton. You will almost always find me with a book. The favorite ways I like to spend my time doing are making family trees, drawing, reading, and watching tv. My ambition when I grow up is to become a fashion designer.

ELLE, AGE: 12

My name is Elle, and I just turned 12 years old. I love cats, and wish I had one of my own. I love to dance, write, sing, read, and draw. I would like to become a lawyer when I am older. My favorite subjects in school have always been ELA and history. I have participated in the science fair all of my life, and I enjoy watching videos and reading articles to better understand the world around me. Fashion is a passion of mine too.

JOSI, AGE: 9

My name is Josi. I love to read and write stories. My favorite animals are pigs because they are really cute. Pink is my favorite color. Science is one of my favorite subjects along with math. For my science project this year, I explored the physics of a scooter because riding my scooter is a favorite activity of mine.

KAVISH, AGE: 9

I am a curious, fun-loving, little fourth grader who is interested in various topics. I like to spend my time writing stories and poems, drawing, singing and dancing. But I love playing above all of them. I love Science and dogs, though my parents don't allow pets. I enjoy observing, experimenting, and discussing all aspects of nature. I would like to become a scientist when I grow up and help the mankind.

AUTHORS

KATHERINE J. LI

Katherine Li is a Ph.D., candidate at Wageningen University & Research and Agroscope. Originally a food toxicologist from Canada, she was introduced to metabolomics during her graduate studies in Colorado and was fascinated with how this tool is able to capture the complexity of food, metabolism, and health. Currently, she is using metabolomics to identify and validate biomarkers of fermented food intake. She is particularly interested in how these biomarkers could eventually be used in personalized nutrition, as well as to improve our understanding of the impact of (fermented) foods on chronic diseases. *katherine.li@wur.nl

KATHRYN J. BURTON-PIMENTEL

Kathryn Burton-Pimentel is a registered dietitian and nutritional researcher who works at Agroscope (Switzerland). Her research uses nutrigenomic tools like metabolomics to help understand why foods can affect people differently. She is particularly interested in how microbes found in some foods (like fermented foods)

and microbes found in the gut interact to affect our health. When she is not behind a computer, she enjoys running, swimming, and hiking.

ELSKE M. BROUWER-BROLSMA

Elske Brouwer-Brolsma is an assistant professor at the Division of Human Nutrition and Health at Wageningen University in The Netherlands. Elske started her career as a dietitian, but soon realized she wanted to dive more into the theory and pursued an M.Sc., in nutritional epidemiology and Ph.D., in nutrition and aging. During that period, Elske became more aware of the caveats of research on nutrition and health, particularly in terms of dietary assessment. As a consequence, Elske decided to dedicate her work to the innovation of dietary assessment methods to improve the quality of research on nutrition and health.

GUY VERGÈRES

Guy Vergères is a Swiss researcher trained in biochemistry whose interest has always been on discovering molecules in foods and how they can promote health. His career path has naturally led him to investigate the interaction of nutrients and foods with the human body. Vergères is a research group leader at Agroscope in Bern, Switzerland. He also teaches nutrigenomics, the modern version of nutrition research, at the ETH in Zurich as well as at the University of Lausanne, Switzerland.

EDITH J. M. FESKENS

Edith Feskens is a professor in nutrition and health at Wageningen University in The Netherlands. She was trained in nutrition and epidemiology and worked for a long time at the National Institute of Public Health in The Netherlands. She is interested in the role of nutrition in the prevention of disease and also in the role of nutrition during pregnancy and growth of children. She is also interested in environmental aspects of nutrition. Her work includes research in South-East Asia and Africa, where both over-nutrition and under-nutrition occur.

frontiers FOR YOUNG MINDS

HUMAN HEALTH
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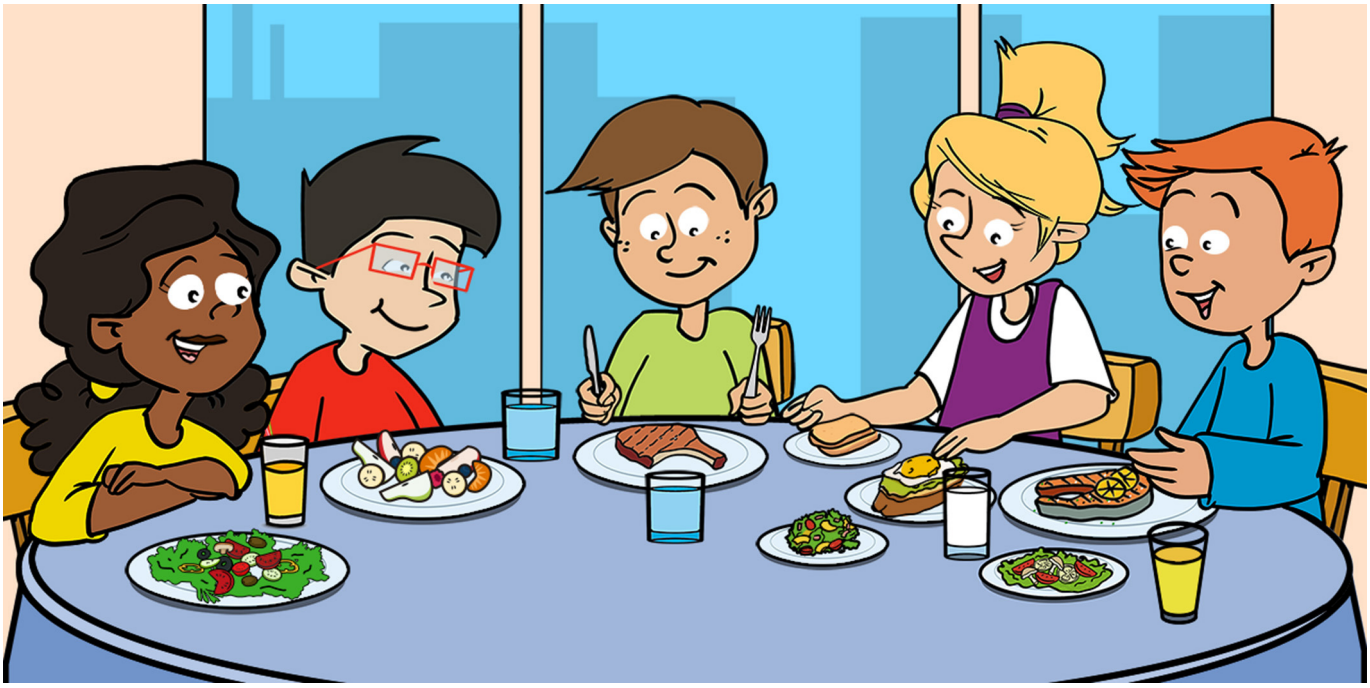

CAN PERSONALIZED NUTRITION IMPROVE PEOPLE'S DIETS?

Katherine M. Livingstone [1]***, Carlos Celis-Morales*** [2,3] ***and John C. Mathers*** [4*]

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YOUNG REVIEWERS:

ETHAN
AGE: 15

SOPHIA
AGE: 13

Each person differs in physical characteristics such as eye color, but also in likes and dislikes. These differences are due to our genes and our environments, including what we eat. What we eat affects our health, and each of us has individual nutritional needs. This is the basis for the idea of personalized nutrition. In our research study, called the Food4Me Study, we tested whether personalized nutrition advice helped over 1,600 people to eat healthier diets. We collected information about each person, including what they ate, and we collected samples of saliva to examine their genes. We gave each person either the usual advice about healthy eating (such as "eat more vegetables") or advice that was personalized based on the individual's characteristics. After 6 months, we discovered that people who received personalized nutrition advice improved their diets more than people who received the typical healthy eating advice.

WHY WE ARE ALL DIFFERENT

Each of us is different. Some people are tall while some are short, some have brown eyes and others blue eyes. We also differ in our likes and dislikes. These individual characteristics make up what is called our **phenotype**, and our phenotypes help to make us the individuals that we are. Differences between individuals are due to a combination of genes and environment, including what people eat. Each of us has small but noticeable differences in our **genes**. The overall pattern of these gene variations is called our **genotype**. For example, height is influenced by hundreds of genes, but is also influenced by what we eat. In general, people are taller when they have been well-nourished at every stage of their development, starting in the womb through their late teens or early twenties, when most people reach their adult heights.

PHENOTYPE

The characteristics of each person including e.g., height, eye color, and behaviors.

GENES

A piece of DNA that provides the information to make a protein. Each of us has more than 20,000 different genes.

GENOTYPE

Small gene variations that are specific to each person.

Identical twins share the same genotype because they come from the same fertilized egg. However, although they have the same exact genes, identical twins are not completely identical. Do you have any friends who are identical twins? If so, can you tell who is who? Twin pairs tend to become less alike as they get older—and not just because they choose to wear different clothes or to style their hair differently! The differences are the result of interactions between each twin's environment (including what they eat) and their genotype, and this combination influences their phenotype.

PERSONALIZED NUTRITION: DO WE ALL NEED TO EAT THE SAME FOODS TO BE HEALTHY?

The ability to eat a wide variety of foods is one of the reasons why humans have been so successful as a species. What we eat affects how well we grow and develop and, of course, our health. Based on the foods that can be grown or found locally, traditional cuisines differ considerably in different parts of the world. So, it seems that people can be healthy without eating the same foods. However, each of us has our own specific nutritional needs because of our genotypes and other individual characteristics. So, some of us would benefit from eating more (or less) of certain foods.

Most of us eat too many sugary, salty, and fatty foods. We would be healthier if we changed what we eat. Although health experts give us excellent advice on healthy eating patterns, this general advice has not been very effective in helping people change their eating behaviors. **Personalized nutrition** is designed to provide dietary advice based on each individual's characteristics [1]. Because it is specific to each individual, we thought that maybe personalized nutrition advice would help people to make appropriate changes to their diets. For example, the genotype of some people indicates that they are

PERSONALIZED NUTRITION

Information about an individual that is used to provide dietary advice specific to that person.

especially sensitive to eating a lot of salt. These people might benefit more from cutting down on salt than other people would. Others might benefit from making certain dietary changes to help them to keep a healthy body weight.

With help from a team of colleagues in several European countries, we set out to test our personalized nutrition idea in a project called the Food4Me Study. In this study, we wanted to find answers to three main questions. First, we wondered whether personalized nutrition is more effective than the usual "one-size-fits-all" dietary advice, when it comes to helping people improve what they eat. We also asked about the best way to develop personalized nutrition advice. Last, we asked whether the internet would be a good method for delivering personalized nutrition advice to lots of people.

OUR DIETARY STUDY

DIETARY STUDY

A special kind of experiment in which researchers investigate how what we eat affects our health and wellbeing.

To answer these questions, we ran a big **dietary study** involving more than 1,600 adults from seven European countries (Figure 1). How did we get enough people to join the Food4Me Study without creating a huge amount of work for the research team? We used the internet! We used posters, radio advertisements, and interviews with senior scientists to encourage people to go to the Food4Me website if they were interested in joining the study. Interested people were asked to fill in online questionnaires to provide information about themselves. We used their answers to identify those people who were suitable for the study [2].

RANDOM ALLOCATION

A process by which people are assigned to experimental groups so that, on average, each group is similar at the start of the experiment.

INTERVENTION

A deliberate change in people's diet to help answer a scientific question.

Next, we placed the participants randomly in one of four groups, in a process called **random allocation**. Random allocation ensured that the people in each group were very similar at the start of the study. Each group was given a different dietary treatment (our **intervention**). People in the control group (group 0) were given the usual healthy-eating advice, for example to eat at least five portions of fruits and vegetables each day. People in groups 1–3 were all given personalized nutrition advice. However, the information used to create the personalized nutrition advice differed for each of these groups. For group 1, we based the advice on an analysis of what each individual ate at the start of the study. For group 2, we used their starting eating pattern plus information on their body measurements, such as waist circumference and blood test results. Finally, for group 3, we based the advice not only on what they ate at the start of the study and their phenotype, but also on their genotype, which we assessed by looking at their saliva. We gave personalized advice based on five genotypes that are known to influence the links between what people eat and their health. For example, we looked at a certain genotype of the gene used to produce a protein called **apolipoprotein E**, which gives people a greater risk of developing heart disease and dementia. People with this genotype would benefit from eating less

APOLIPOPROTEIN E

A blood protein that helps transport cholesterol and other fats. A variant of the gene for apolipoprotein E gives some people a greater risk of developing heart disease and dementia.

Figure 1

Over 1,600 individuals from seven European countries were included in the Food4Me Study.

Figure 1

saturated fat, the "unhealthy" fat found in high amounts in foods like sausages and cakes. For each person in groups 1–3, we provided personalized advice designed to help them make dietary changes that were directly relevant to them and that would hopefully improve their long-term health.

To find out whether people in personalized nutrition groups 1– 3 made bigger improvements in their diets than those in group 0, we collected information on what each person ate at the start of the study, and again 6 months later. Study participants helped us with this by filling in detailed food-frequency questionnaires on the Food4Me website. These questionnaires asked them how often they ate over 150 different common foods and drinks, such as fruits and vegetables, cheese, yogurt, and fizzy drinks, and how much of each these foods they ate. We could then then determine whether our advice helped people improve their diets by eating more healthy foods and less unhealthy foods. The data participants provided was analyzed automatically by computer, which saved a huge amount of time and effort compared with paper forms [2].

WHAT DID WE DISCOVER IN THE FOOD4ME STUDY?

At the end of the Food4Me Study, we found that our participants' eating habits improved, which was good news. However, there were bigger improvements for people in groups 1–3 than in group 0. The improvements were similar in groups 1, 2, and 3, which told us that the specific dietary information given to each group was not as

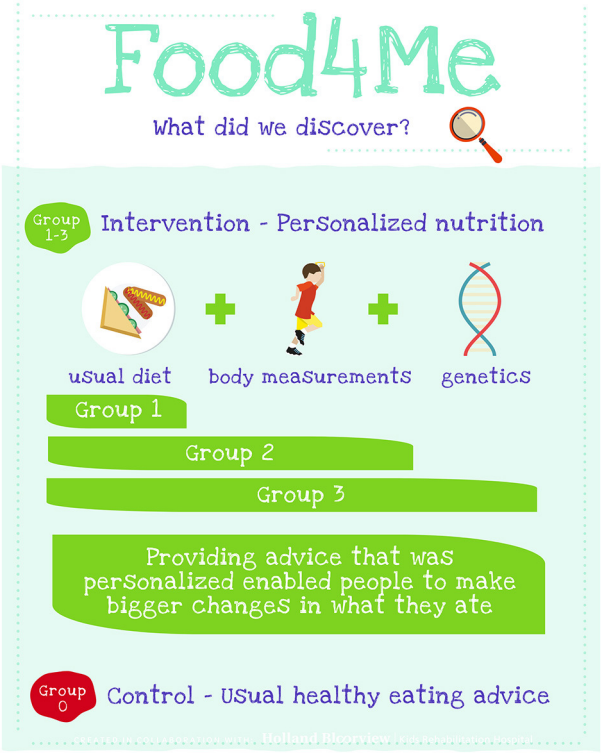

Figure 2

Summary of discoveries in the Food4Me Study. Our intervention made deliberate changes to dietary advice to see if it improved eating habits. The personalized advice given to Group 1 was based on each participant's diet at the start of the study; Group 2 was based on their diet and their phenotype, and Group 3 was based on their diet, phenotype and genotype. These three groups were compared with the control group, which was given general advice on healthy eating.

important as the fact that the advice was *personalized* [3]. Personalized dietary advice helped people to make bigger dietary changes than when the advice was not personalized (Figure 2). The Food4Me Study also showed that it was very practical to use the internet to deliver personalized nutrition advice to lots of people who lived in different countries [3].

COULD PERSONALIZED NUTRITION IMPROVE EVERYONE'S HEALTH?

What we eat really matters. Alongside being physically active and not smoking, healthy eating habits are one of the most important ways to stay healthy throughout our entire lives. However, most people ignore healthy eating advice. This can eventually lead to a wide range of health problems, such as obesity, heart disease, and diabetes. Could we use what we have discovered in the Food4Me Study to improve *everyone's* eating habits and help all people stay healthy? Well, it is clear that personalized nutrition advice helped people to make bigger improvements in their diets than non-personalized advice did [3], and other studies have discovered this, too [4].

Although Food4Me was a rather large study involving more than 1,600 people in seven European countries, to improve the health of *everyone* in Europe, we would need to deliver personalized nutrition

advice to hundreds of millions of people! This is an enormous challenge, because we would need to collect and analyse genotypes and dietary information for each person in the population. However, in the Food4Me Study, we developed computerized systems called **algorithms** that make it much easier to make personalized nutrition advice available to everyone. We have seen that people across Europe are keen to use personalized nutrition advice and that they are happy to use the internet to get this information. The next big challenge is to scale up the Food4Me approach and test it on many more people, to see if it can potentially help us all develop healthier eating habits.

ALGORITHMS

A set of rules used by a computer used to carry out calculations or to solve complex problems.

ORIGINAL SOURCE ARTICLE

Celis-Morales, C., Livingstone, K. M., Marsaux, C. F. M., Macready, A. L., Fallaize, R., O'Donovan, C. B., et al. 2016. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. *Int. J. Epidemiol.* 46:578–88. doi: 10.1093/ije/dyw186

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YOUNG REVIEWERS

ETHAN, AGE: 15
Hi! my name is Ethan. At my regional science fair, I won Best Junior Project, Best Biology Project, Gold Medal, and a qualification to the Canada-Wide Science Fair, where I achieved a bronze medal. I have also been a finalist at the InspoScience Canada IRIC. Besides, I enjoy debating, having won the title of national champion and second speaker this past year, and public speaking. I am an avid writer, being published for my poems, short stories, and argumentative articles.

SOPHIA, AGE: 13
My name is Sophia, I am 13 years old. I live am Brazilian and love to play with my friends and watch videos on the internet.

AUTHORS

KATHERINE M. LIVINGSTONE
Katherine M. Livingstone is a senior research fellow in the Institute for Physical Activity and Nutrition at Deakin University in Australia. She completed her Ph.D. in nutrition at the University of Reading in the UK. Katherine leads personalized nutrition research to improve the diets of adults. She is passionate about understanding how our biology and behaviors influence our food choices and our health, so that we can design more effective dietary interventions and healthy-eating policies. Katherine's research was funded by a National Health and Medical Research Council Investigator Grant.

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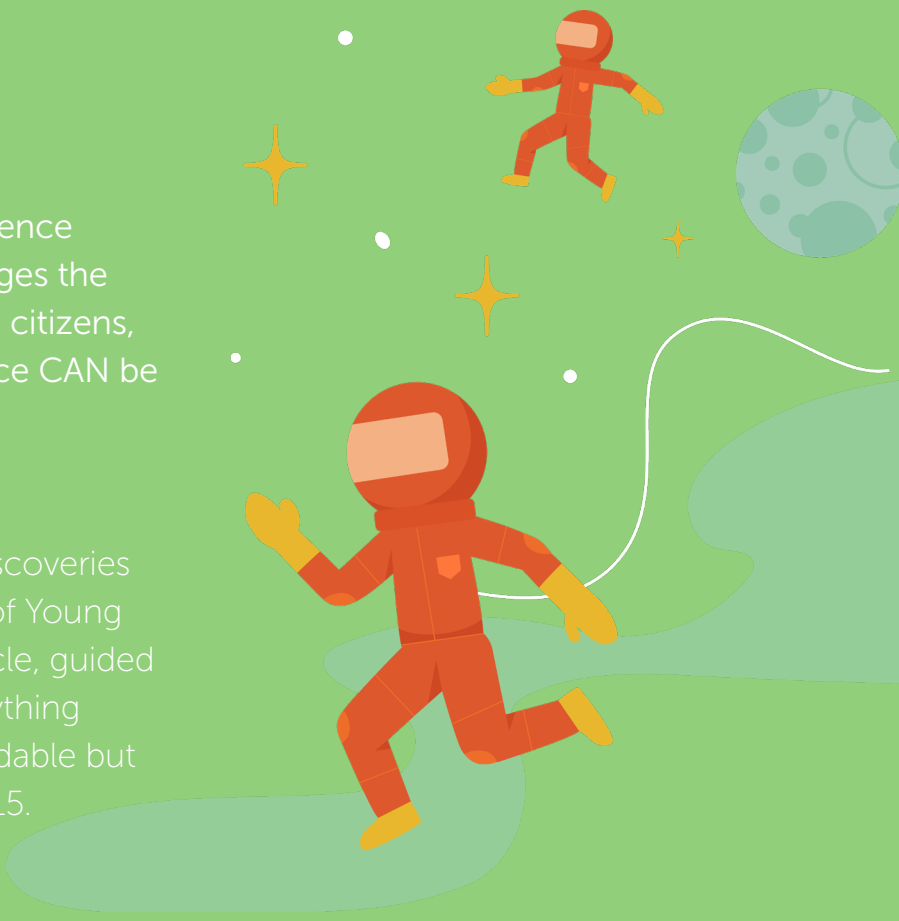
Carlos Celis-Morales is a senior research fellow at the Institute of Cardiovascular and Medical Sciences at the University of Glasgow. He is also an associate professor at the Research Unit in Education, Physical Activity and Health at the University Católica del Maule in Chile. His research interests focus on the role of lifestyle (nutrition, physical activity, sleep, and smoking) in preventing chronic diseases such as obesity, type 2 diabetes, hypertension, heart diseases, and cancer. In addition, he has worked for many years on personalized nutrition to improve lifestyles, behaviors, and health.

JOHN C. MATHERS

John C. Mathers is Professor of Human Nutrition at Newcastle University in the UK. In addition to teaching students about nutrition and health, he carries out research on nutrition and aging and on the risk of age-related diseases. He was one of the founding members of NuGO—the European Nutrigenomics Organization—that has pioneered the use of modern molecular methods for studying how what we eat affects our health. John is also interested in finding better ways, such as using digital and personalized approaches, to help people eat better diets and to improve their health. *john.mathers@newcastle.ac.uk

Frontiers for Young Minds



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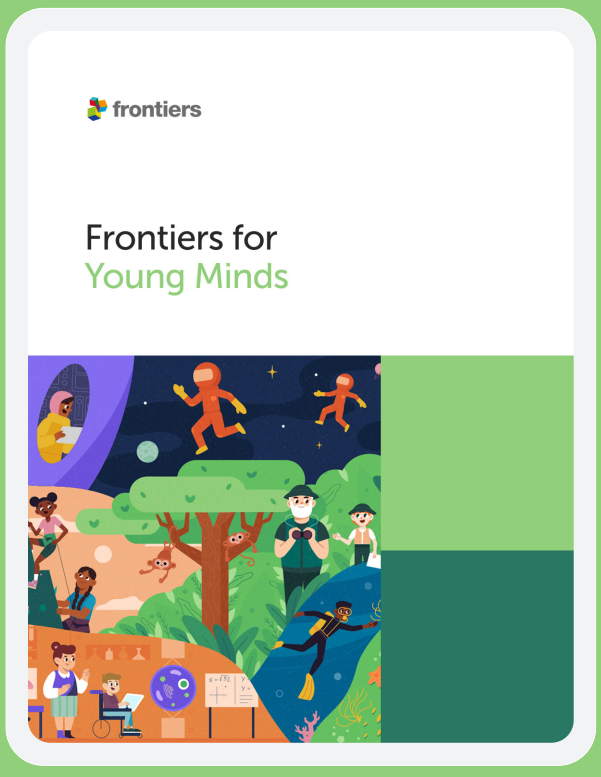

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