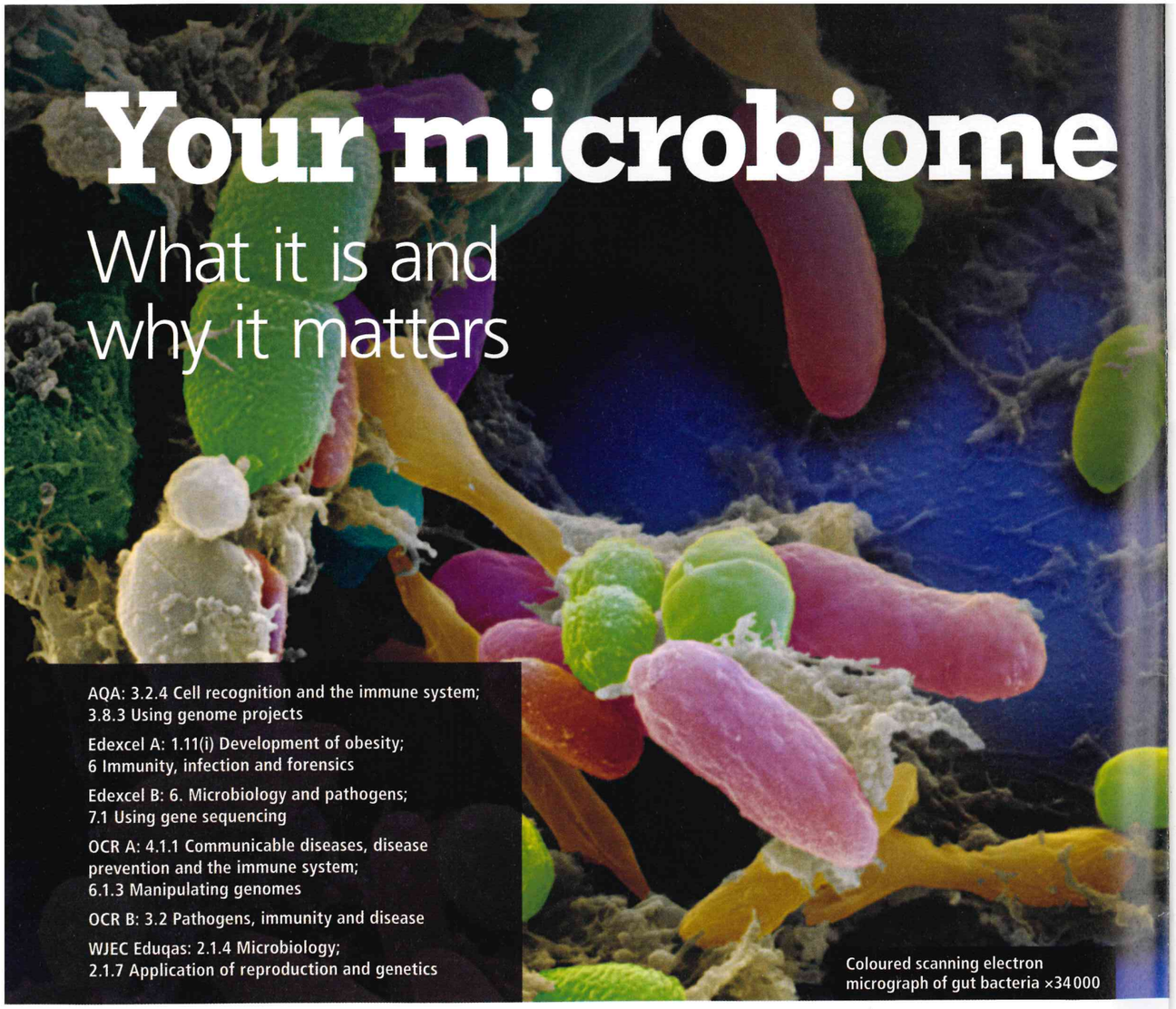
Your microbiome

What it is and why it matters



Coloured scanning electron micrograph of gut bacteria ×34 000

AQA: 3.2.4 Cell recognition and the immune system; 3.8.3 Using genome projects

Edexcel A: 1.11(i) Development of obesity; 6 Immunity, infection and forensics

Edexcel B: 6. Microbiology and pathogens; 7.1 Using gene sequencing

OCR A: 4.1.1 Communicable diseases, disease prevention and the immune system; 6.1.3 Manipulating genomes

OCR B: 3.2 Pathogens, immunity and disease

WJEC Eduqas: 2.1.4 Microbiology; 2.1.7 Application of reproduction and genetics

Elle Lindsay

The microorganisms living on and in your body play an important role in your biology and possibly even your mental health. Doctoral researcher Elle Lindsay explains

You might not think of your body as a habitat, but trillions of microorganisms including bacteria, fungi and viruses thrive in the environment you provide. Researchers call these microorganisms your **microbiome** (or **microbiota**). They outnumber your own cells 10 to 1. They occur throughout your body, for example in your gastrointestinal tract, on your skin and in your lungs (see Figure 1).

Key words

Ecological community
Microbiota
Microorganisms

Microorganisms are present in all sites on your body that have sustained contact with the external environment. The most diverse sites include the gut, the nostrils and the vagina, the least diverse the elbow and the palm of the hand. The density of microbes also differs depending on location. Microorganisms are particularly dense around hair follicles.

The bulk these organisms represent is considerable. The volume of the human microbiome is 1.5 dm^3, with a mass of approximately 1 kg. Our relationship with our own microbiome is remarkably complex and we are only just beginning to understand the scope of these interactions and how they contribute to our wellbeing and survival.

The microbes you're born with

We are born with a microbiome already in place. Microorganisms are picked up via the birth canal and later through skin contact. Breast milk also provides microorganisms that populate a baby's gut, so the microbiota diversifies from the first few weeks of life. For the rest of our lives we come into contact with microbes from all kinds of sources, including other people, animals, food and soil.

These diverse inputs mean that microorganism communities are remarkably variable, even between individuals of the same age. The microbiota we host differ due to factors including our age, gender, occupation, hygiene and genes. They vary more between two different parts of our own body than between the same location on two different people. There are remarkable differences, for example, between microorganisms found in the gut and those found on our feet.

The method of birth, whether vaginal or by caesarean section (C-section), impacts the infant microbiota. Babies delivered vaginally have microbiota dominated initially by *Lactobacillus*, whereas that of babies delivered by C-section is dominated by *Staphylococci* — closely matching the maternal skin. A newborn that has passed through the birth canal ingests the wide variety of bacteria present in vaginal secretions and faeces, while C-sections result in newborns being colonised by bacteria from the tools used during surgery and the mother's skin. The microbiome of a baby born by C-section is therefore much less diverse than that of a baby born vaginally. It is thought that the microbiome formed via contact with the birth canal helps build the immune system and improve digestive efficiency better than the microbiome resulting from C-sections.

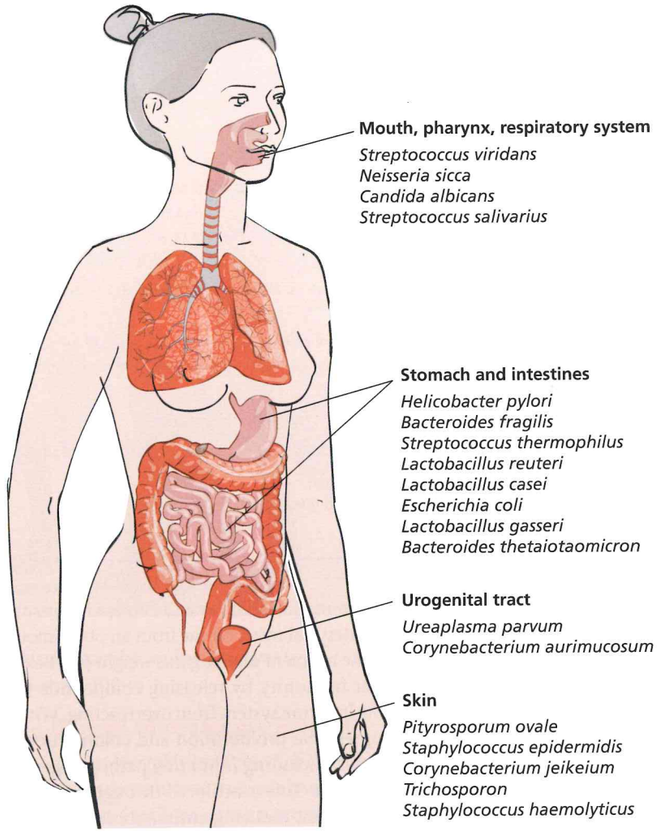


Figure 1 Microorganisms present at different body sites

Good, bad and indifferent microbes

The good

Microbes and humans have a long history of cooperating with one another. Some microbial genes directly benefit us and other species, as they code for enzymes that hydrolyse food we are incapable of digesting alone, or code for proteins that form essential nutrients. Microbes within our large intestine make vitamins we can't produce, such as B vitamins, which are important in DNA synthesis and repair. Gut microbes also help release energy from fats and proteins in our diet, allowing us to convert more energy from the food we eat. Molecules made by gut microbes enter the blood stream and perform a variety of functions. They can stimulate our cells to store energy as fat or glycogen, they determine how we respond to insulin and can even regulate appetite and weight gain.

The diversity of intestinal microorganism communities in obese individuals differs from that of lean individuals. Obese people have a higher proportion of **Gram-negative** to **Gram-positive** microbes in their guts. This increases the concentration of lipopolysaccharides, which has

The microbiome of newborn babies is partly determined by the method of their delivery

Terms explained

Colonisation Microorganisms growing in an environment.

Commensal A relationship in which one organism benefits and the other remains unaffected.

Enteric pathogen Pathogen in the gut.

Gram-positive/Gram-negative Gram-positive bacteria have one cell surface membrane and a thick cell wall. Gram-negative bacteria have a thin cell wall and an additional outermost membrane. The name refers to whether or not they stain with crystal violet.

Metagenome All the genetic material within an environment, from all the many organisms present.

Microbiome The microbial community, or microbiota, present, as well as their genomes. (Biomes are distinct biological communities that occupy a physical habitat, e.g. our bodies.)

Microbiota A community of microorganisms found in one location.

Personalised medicine Medical treatments tailored to the patient based on his/her individual needs, responses and risks.

Probiotics Live microorganisms ingested to give health benefits.

Proliferation Rapid increase in number.

Box 1 Germ-free animals

In the laboratory it is possible to produce animals free from microorganisms ('germ-free'). These animals allow scientists to go beyond correlation and prove cause and effect. For example, bacterial species in the gut of an obese mouse might be there by chance, as the result of a rich diet. Showing that you can transfer gut bacteria from an obese mouse into a germ-free mouse and cause it to become obese is far more compelling evidence that microbes contribute to obesity (see Figure 2).

been shown to generate chronic inflammation in mice and can lead to insulin resistance. Figure 2 shows that if the intestinal microbiome from an obese mouse donor colonises a germ-free mouse, the recipient mouse gains weight (see Box 1).

Other microorganisms affect our immunity by releasing compounds that reduce inflammation and prevent the immune system from overreacting. Within the gut, **commensal** microbes suppress the **proliferation** and **colonisation** of **enteric pathogens** in a variety of ways, including inhibiting pathogen growth and increasing the host's barrier function. This is achieved through increasing the thickness of the mucus layer in the gut, inducing antimicrobial molecules and regulating antibody secretion.

The bad

Many health conditions, including acne, dental caries, obesity, gastric ulcers and asthma, involve your microbiome. The microbiome is thought to be intimately associated with Crohn's disease — a chronic inflammatory condition affecting the gut. In people with Crohn's disease, microbial diversity in the gut is reduced. This may affect immune interactions, as there are fewer kinds of microbes to carry out the vast array of beneficial tasks that occur in a healthy individual. It is also thought that many of the bacteria in Crohn's patients invade the intestinal wall and cause inflammation.

Studies are currently being carried out to determine the gut microbiome community structure in Crohn's patients in comparison to healthy individuals. A greater understanding of which microorganisms are overrepresented or underrepresented in affected individuals and how this impacts their health will allow new treatments to be developed.

The indifferent

The vast majority of microbes in our biome appear to be harmless. Most are simply living there because our internal and external environments suit their requirements. Determining the exact role of a microbe in our bodies is challenging, as many studies find tantalising correlations, but show no solid links between cause and effect.

With such a wide variety of microbes present, it is difficult to identify the function of any specific one. The only way to know for sure is to see the effect of removing that microbe, but targeted

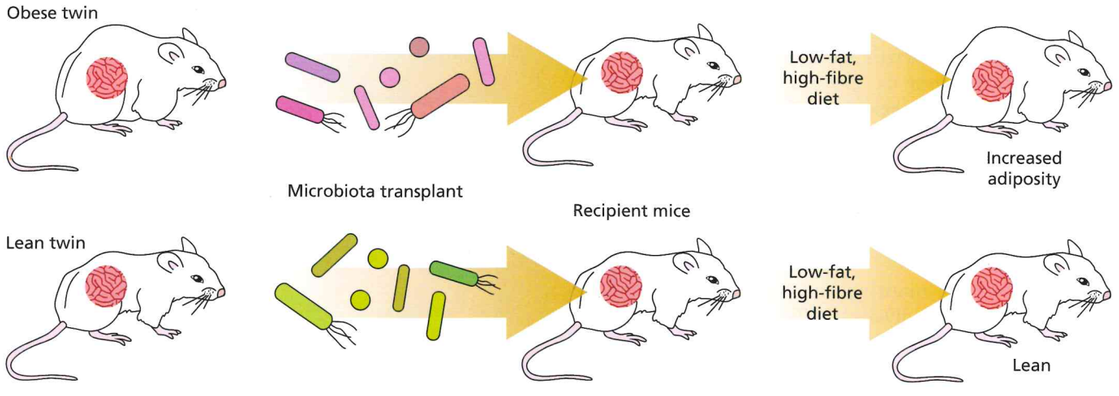


Figure 2 Transplanting microbiota to 'germ-free' mice bred in the laboratory can demonstrate the role of gut microbes in obesity


Hadza hunter-gatherers of Tanzania. The Human Microbiome Project has studied their microbiome

removal of one species is often impossible. The microbiome is dynamic and there are microbe–microbe interactions as well as host–microbe interactions and environmental effects (such as pH, temperature and diet). This means many relationships must be taken into account when trying to ascertain function.

Next-generation DNA sequencing

In order to understand our own personal ecosystem, we must first identify all the different bacteria, eukaryotes and viruses that make up our microbiome. In the past, this was an almost impossible task, and could only be achieved by culturing and then identifying individual bacteria in the laboratory. A single 1 g faecal sample might contain 1 billion individuals of 20 000 different species. Identifying these using traditional approaches would be a lifetime's work. Until recently DNA sequencing methods did not allow assessment of more than one DNA sequence at a time. This meant having to culture each bacterial species in clonal cultures, where all of the cells present and their DNA are identical. Furthermore, many (if not most) bacteria have complex growth requirements and cannot be cultured at all.

Next-generation sequencing has made the study of microbiomes possible (see Box 2). We can now read millions of DNA sequences directly from millions of bacteria without culturing them first, and then use powerful computer algorithms to sift through the terabytes of data generated. This research has shown that bacterial genes in your body outnumber your own by a massive 100 to 1.

The Human Microbiome Project

The Human Microbiome Project (HMP) began in 2008. The aim was to map the human microbiome and analyse how it interacts with human health and disease. The HMP has characterised the different microbial communities throughout the body, in different age groups, in men and women, in developed and developing worlds, and between metropolitan elites and Hadza hunter-gatherers of Tanzania. The HMP aims to answer questions such as whether there is a 'core' microbiome at each site in the body, and to understand the relationship between lifestyle, diet and disease, and changes in the human microbiome.

Huge progress has been made in characterising the human microbiome, and there are many potential lines of inquiry that could be pursued as research

Box 2 Next-generation sequencing

Next-generation methods available for sequencing DNA and RNA are also known as 'high-throughput sequencing'. These are more efficient and quicker than previous sequencing approaches.

Sequencing tells us the order of nucleotides in the section of DNA being studied. This can be beneficial when trying to identify unknown species or in medical diagnosis of genetic conditions (see Further reading for a video).

- A machine 'reads' the sequences of millions of strands of DNA molecules at the same time.
- The DNA molecules of interest are cleaved into short strands, amplified and separated into single strands to be read. Nucleotides with fluorescent labels are added, with each nucleotide base having a different colour.
- These labelled nucleotides use the single stranded DNA template to form a complementary DNA strand. Due to the fluorescent labels, the sequencing machine detects the order in which the bases were added. This results in the DNA sequence.

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continues. As understanding increases, so too does the number of questions about the microbiome and its role as helper or hindrance. Big questions must be explored, including which features are inherited, whether microbial taxonomic groups are being lost and gained on evolutionary timescales and whether the **metagenome** can predict risks for specific human diseases. New frontiers are opening up daily.

Mental disorders

There are suggestions that gut bacteria stimulate the brain via the vagus nerve, which is a collection of approximately 500 million neurones that form the backbone of the parasympathetic nervous system (see Figure 3). Gut bacteria make some of the molecules that stimulate the brain, including GABA, serotonin and acetylcholine. This may be why links have been found between microbe-related intestinal disorders and mental illnesses such as anxiety and depression. Our understanding is in its infancy, but future treatments for these disorders could potentially stem from manipulating gut microbes.

Faecal microbiota transplants

Stool bacteria can be transferred from a healthy donor into a diseased recipient, in an attempt to restore healthy colonic microbiota. Such faecal microbiota transplants have been successful in patients suffering from *Clostridium difficile* infection, which causes diarrhoea, fever, nausea and abdominal pain. Research is investigating whether such transplants can be used to help other non-gastroenterologic conditions such as Parkinson's disease and obesity.

Diagnosing disease

As our understanding of host-microbiome interactions grows, so too will our ability to diagnose diseases. Associations between human conditions and particular microbiota characteristics are appearing. For example, obese individuals have a reduced ratio of Bacteroidetes to Firmicutes, and people with inflammatory bowel disease have been found to have larger populations of Enterobacteriaceae.

In the future microbiome monitoring in medicine might be used to diagnose disease, predict prognoses, create personalised dietary interventions and lead to increased use of **probiotics** to regain a healthy microbiome. Enhanced understanding should also help determine how to manipulate the microbiota to reap health benefits and herald a new era of **personalised medicine**. The possible areas of investigation seem limitless and rather overwhelming at the moment but in time this frontier could revolutionise the way we look at the human ecosystem.

Points for discussion

- The microbiome of an organism changes over time. How could we find out if flexibility in the microbial community composition helps the host individual adapt to changing environments?

Further reading

Learn Genetics page on the human microbiome: **www.tinyurl.com/nutgszy**

Video from Brown University about the human microbiome: **www.youtube.com/watch?v=ugg3Jynib6g**

The Human Microbiome Project: **https://hmpdacc.org/**

Next-generation sequencing explained: **www.youtube.com/watch?v=ToKUGz_YhC4**

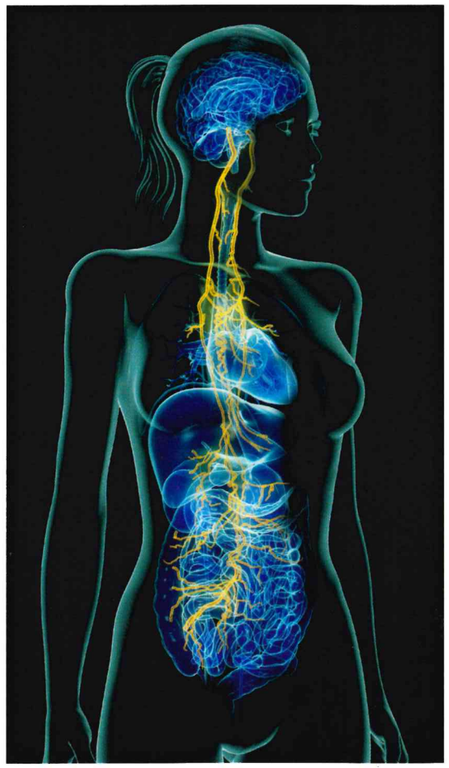

Figure 3 The brain–gut axis: potential interactions between the gut microbiota and the central and peripheral nervous systems

- Some bacteria are found to be inherently harmful to the host. How could we alter microbiota to replace harmful bacteria with helpful species?

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Key points

- The human body does not function in isolation. We are home to many microbes, some of which help us function.
- Some of our microbes appear to have no effect on us, others generate health conditions including obesity, intestinal and mental disorders.
- Just as the microbes affect us, we have an impact on the microbes, which results in differences in the microbial species present on different parts of the human body.
- We already manipulate our microbial communities to give us health benefits, and current research will extend our ability to do this.

The Atlantic ghost crab

What distinguishes this crustacean, and why is its distribution in decline?

You may have found crabs in rock pools or have caught them from the sea using bait on a fishing line. As a result, you might think that crabs are aquatic animals. But although the Atlantic ghost crab shown in this picture is near the sea, the adult animals are terrestrial, living in burrows that they dig in the sand. These burrows can be over a metre deep and are usually above the intertidal zone. Burrows of old adults have been found in sand dunes over 300 metres inland from the sea.

Adults are generally active at night and are omnivores, feeding on shellfish, insects, plant material and even each other. They can swivel their prominent, stalked eyes through 360°, giving them all-round vision. They communicate by hitting the sand with their large, white claws. Like all crustaceans, the gas exchange system of the Atlantic ghost crab consists of gills. Although the proportion of oxygen in air is around 21% and in sea water less than 1%, without the support of water the crab's gills collapse, severely reducing its surface area for gas exchange.

So although adult crabs spend most of their time on land, they are often seen scuttling to the retreating surf, where they moisten their gills. They also release their larvae into the sea.

Sadly, human affection for sandy beaches has led to a decline in distribution of ghost crab populations. Walking and driving vehicles on beaches can crush the crabs. It also causes compression of the sand, which makes it unsuitable for burrowing and reduces the crab's food supply. As a result, populations of Atlantic ghost crabs are mainly restricted to inaccessible beaches.

Martin Rowland and Geremis Luces

Ghost crab (*Ocypode quadrata*)