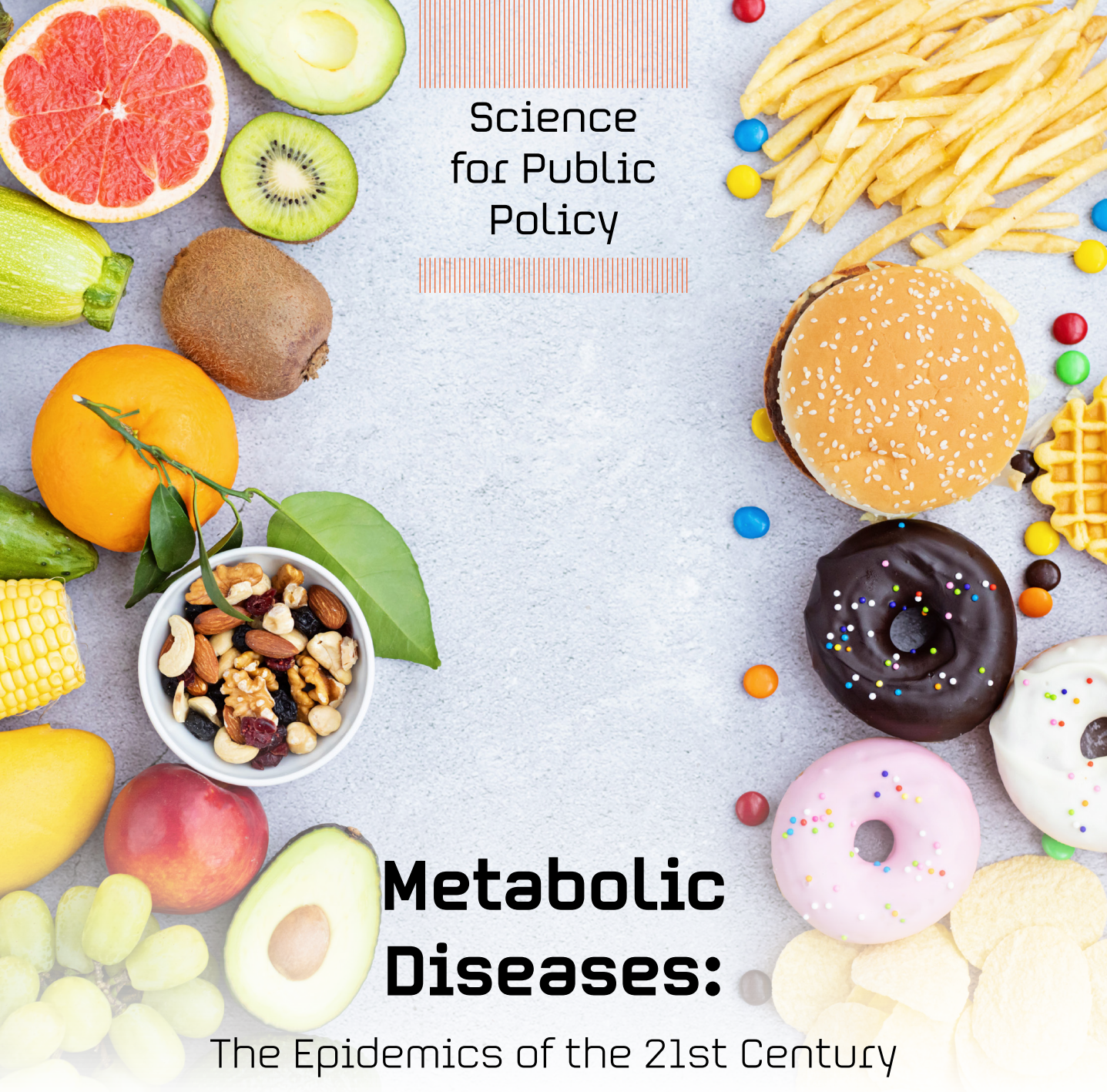

Science for Public Policy

Metabolic Diseases:

The Epidemics of the 21st Century

Coordinated by:
Germán Perdomo Hernández · Marc Liesa Roig · M.ª Ángeles Martín Arribas
Ángela M.ª Martínez Valverde · María Monsalve Pérez · Yolanda Sanz

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One of the CSIC's functions is to inform, assist and advise public and private entities on science and technology, as stated in article 5 of its Articles of Association. As part of this role, the report entitled *Metabolic Diseases: Epidemics of the 21st Century*, from the Science for Public Policy collection, is presented as a document aimed at public administrations and society in general. This report analyses the social, health and economic problem posed by the increase in obesity, type 2 diabetes and cardiovascular diseases, aggravated by lifestyle and exposure to environmental risk factors. Finally, it addresses the organisation's most important lines of research to solve the current challenges of metabolic diseases, with the aim of promoting the transfer of the basic knowledge generated at the CSIC to companies, the public sector and society.

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one

Metabolic Diseases

Four main groups of diseases account for 74% of deaths worldwide: cardiovascular diseases, cancer, chronic respiratory diseases and diabetes. Among these, cardiovascular diseases and diabetes account for almost half of all deaths (about 20 million people per year). Obesity is one of the most important risk factors for the development of cardiovascular disease and diabetes. Metabolic diseases (obesity, diabetes and cardiovascular disease) therefore represent a major global health and social problem.

ADOBE STOCK

1.1.

Introduction: social, political and scientific relevance

Metabolic diseases result from a combination of genetic, physiological, environmental and behavioural factors. Three risk factors explain their increase in recent years:

- Risk behaviours: smoking and alcohol consumption, physical inactivity and high intake of easily accessible unhealthy foods.
- Genetic propensity to develop high blood pressure, high blood sugar and fat levels, overweight and obesity.
- Environmental risk factors: mainly air pollution, light pollution, food additives, as well as other chemical compounds in the diet whose contribution to metabolic disorders that may cause obesity and hyperglycaemia have not been adequately assessed.

These risk factors are compounded by deficiencies in prevention measures, as well as in early detection, access to treatment and care for people suffering from these diseases. **The aim of the report *Metabolic Diseases: Epidemics of the 21st Century* is to convey to society the research being carried out by the CSIC to prevent and control the risk factors, and understand the origin of metabolic diseases.**

Metabolic diseases are now considered an epidemic with devastating consequences for individuals, their families and communities, and a threat to health systems through the risk of saturation and socio-economic costs. Prevention, risk factor management, patient care and surveillance of these diseases are a major priority for the 21st century.

One of the missions of the World Health Organisation (WHO) is to provide leadership and the scientific basis for international surveillance, prevention and control of metabolic diseases. In this regard, governments need to act, following WHO guidelines, to achieve global targets for reducing the burden of disease caused by metabolic diseases. Countries should provide the necessary material and human resources to prevent the onset of these diseases and to reverse the widespread increase in deaths and disabilities caused by such diseases. The implementation of this set of measures could help to make decisions based on scientific evidence and to monitor and evaluate progress in combating metabolic diseases. In this regard, even **the 2030 Agenda for Sustainable Development** includes, as one of the main targets, the reduction of deaths from cardiovascular diseases and type 2 diabetes by one third.

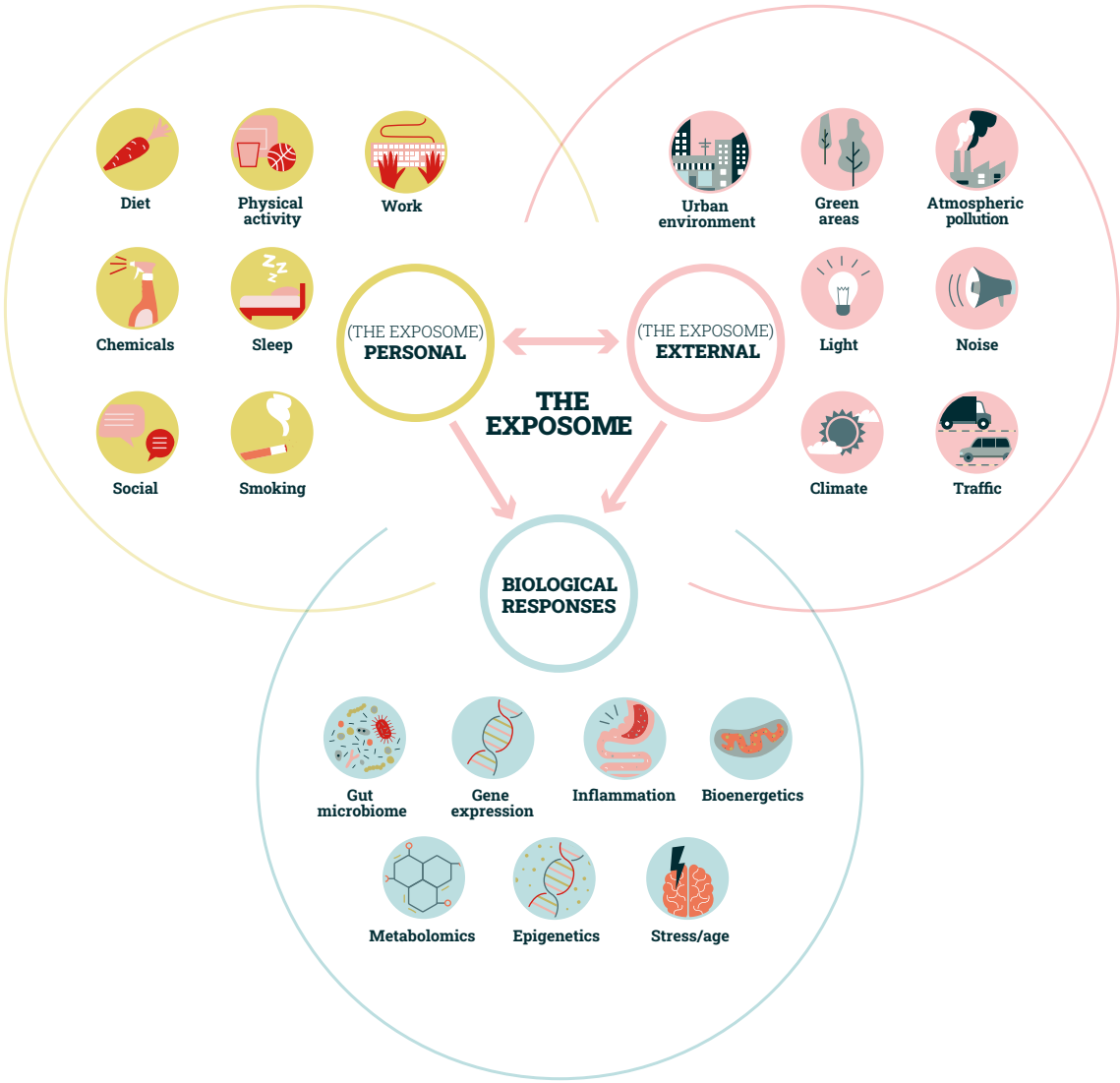
Currently, great emphasis is placed on reducing modifiable risk behaviours such as diet, lack of exercise, smoking and excessive alcohol consumption to prevent and control metabolic diseases. In relation to these factors, it is relevant to highlight two reports in the 2023 *Science for Public Policy* series produced by CSIC researchers. The report ***Producing Food without Depleting the Planet*** explains the current food crisis of a changing planet in food supply, the factors that have caused it and its consequences. The report ***Sustainable and Healthy Nutrition*** explains the challenge of establishing responsible nutrition and food consumption globally, as well as the need to mitigate the poor distribution of resources, which leads to the risk of undernutrition in some areas and overnutrition in others, all of which is aggravated by environmental and geopolitical crises.

However, the environmental components to which we are exposed, known as the exposome, also have a major impact on our metabolism. The exposome is defined as the set of environmental stressors that amplify the impact of risk behaviour on metabolic diseases. In 2012, a WHO study estimated that 23% of all deaths could be attributed to the environment and identified environmental pollution as the main cause. The same work also identified air pollution as the most important type of stressor and correlated it, along with exposure to tobacco smoke, with an increased risk of obesity, type 2 diabetes and cardiovascular disease.

Another example of the importance of environmental factors is exposure to light pollution (see the report ***Light Pollution*** in the Science for Public Policy 2024 collection), which can disrupt individuals' circadian rhythms (the biological parameters that vary depending on whether it is day or night) and normal metabolic cycles, increasing the risk of metabolic diseases.

Similarly, the report ***Combating Plastic Pollution*** (from the 2023 report series) analyses the environmental and health problem posed by microplastics and outlines strategies to reduce pollution. Some of the chemicals in the plastic products we use every day can disrupt our endocrine system and lead to the development of metabolic disorders such as obesity and type 2 diabetes.

Figure 1 Effect of the exposome on the biological responses that cause metabolic diseases



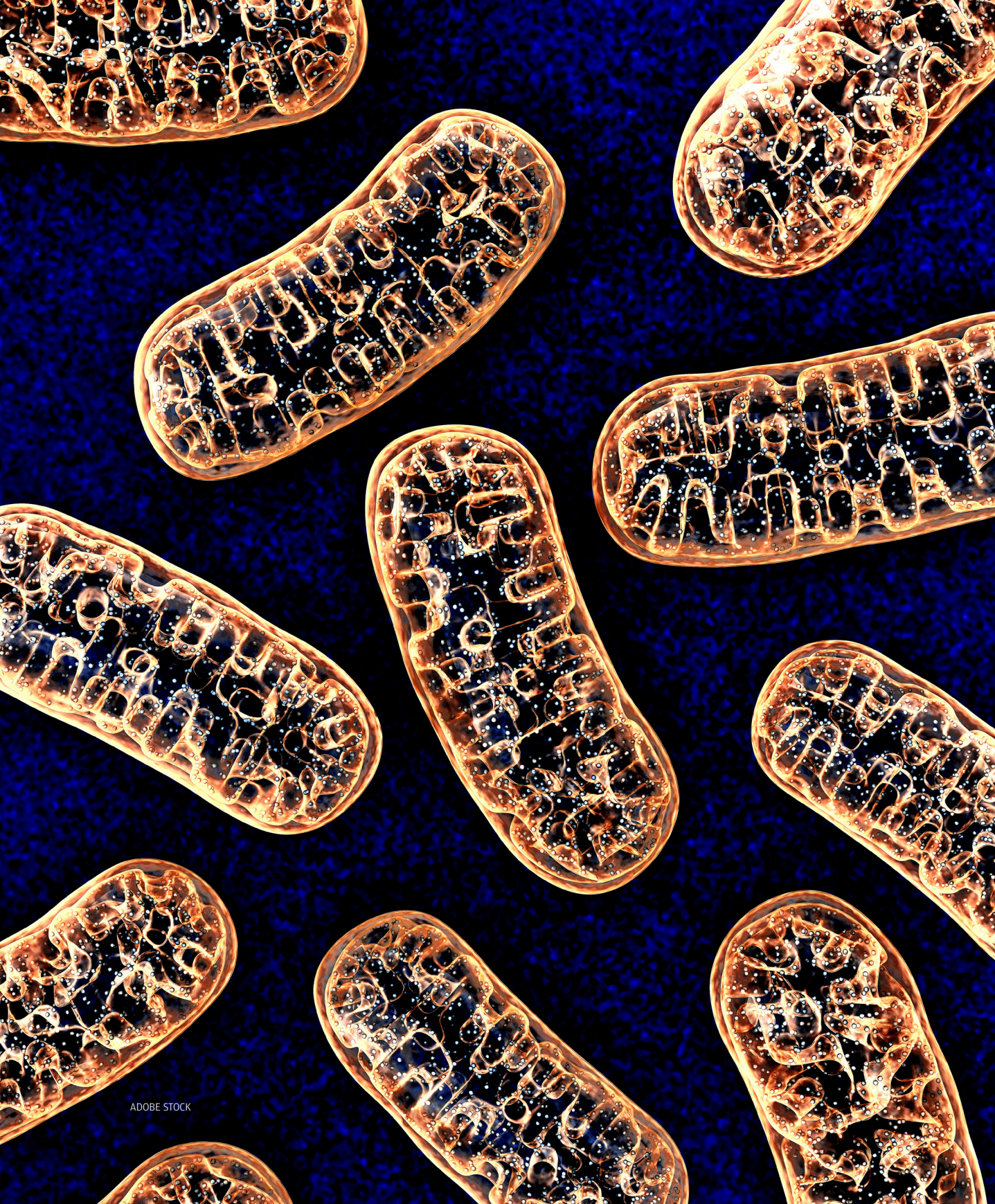
12.

What is metabolism, what is it for and how is it regulated?

Living beings need energy to maintain basic functions such as heartbeat, body temperature, tissue repair, physical and mental activity, among others. Our body has the ability to obtain energy from food nutrients. Calories are a measure of the energy found in food. From these nutrients we also obtain the molecules that form part of our body and replace worn-out molecules. Metabolism is the set of processes that our body carries out to obtain from nutrients, energy and the necessary molecules that keep us healthy.

The main types of nutrients contained in food are carbohydrates (including sugars), lipids (fats) and proteins. After a meal, our body uses the nutrients it needs at that moment and stores the surplus mostly as fat and, to a lesser extent, as glycogen. In fasting or food shortage situations, the stored nutrients maintain our vital functions. An adult person weighing around 65 kilos needs around 1,800 to 2,000 calories per day. Approximately 60% of food intake is used to maintain the structures and functions of the body, 30% for physical activity and 10% is spent as heat and serves to maintain body temperature. The brain is the most energy-consuming organ and is dependent on carbohydrates. Following the brain, the heart is the organ with the highest energy requirement, using mainly lipids, although it can also employ carbohydrates.

When food is ingested, it is broken down in the digestive tract into individual molecules, such as glucose. This allows glucose to enter the bloodstream and be detected by the pancreas, which responds by secreting the hormone insulin. Insulin causes tissues such as muscle and fat tissue to take up glucose from the blood and use it as needed. The liver is an organ that chiefly performs two functions when we eat food: on the one hand, it stores excess glucose in the form of glycogen, and on the other hand, it converts glucose into lipids (fats) that are transported and stored in adipose tissue. Lipids are also obtained through food intake and are transported and stored in adipose tissue.



ADOBE STOCK

In the absence of food (fasting state), the pancreas detects a drop in the amount of blood glucose, which stops the secretion of insulin. Low blood glucose levels trigger the secretion of the hormone glucagon in the pancreas. Glucagon has two main functions: to convert glycogen stored in the liver into glucose molecules that are distributed through the blood to the whole body; and to activate the release of lipids stored in adipose tissue into the bloodstream for metabolism by the liver for energy. This illustrates the generosity of the liver, which always uses nutrients according to the body's needs. It also demonstrates that the levels and activity of pancreatic hormones (insulin and glucagon) are critical in regulating metabolism. Finally, the very lipids released by adipose tissue can be used by our body as a source of energy during periods of fasting.

The processes that regulate our body's metabolism are much more complex than described in this report. For example, biorhythms (cycles of light and dark) mark periods of intake and activity (during the day) and periods of fasting and inactivity (during the night). In this way, biorhythms regulate our body's metabolism. If the biorhythms are disturbed, our metabolism can become dysregulated and this can have negative consequences for our health. Another example of great importance for metabolism regulation is our brain, which produces hormones that control our appetite and satiety. Thus, social, psychological factors or emotional stress can cause eating disorders such as anorexia or bulimia.

How is energy obtained from nutrients?

Obtaining energy from the lipids stored in our body is a slow and complex process, but it allows us to respond to prolonged effort over time. In contrast, stored carbohydrates allow a rapid response to a sudden need for energy, for example, during a sprint or when lifting weights. Mitochondria are cellular structures responsible for extracting the energy needed to sustain life from nutrients, consuming 80%-90% of the oxygen we breathe to perform this function. Mitochondria are activated mainly during periods of fasting or when our body's energy demands are very high. In addition to their bioenergetic role, they also participate in metabolic reactions by synthesising many of the structural and functional components of our body, as well as some hormones. Mitochondria also protect us from damage caused by all kinds of agents, including virus and bacterial infections. They are likewise able to integrate signals that indicate that a cell is deteriorating, triggering cell death mechanisms to prevent damage to our bodies, as in the case of cancer cells. Finally, maintaining mitochondrial function is essential for healthy ageing and for preventing metabolic diseases. There is currently a great deal of interest in understanding how mitochondria operate and how they are repaired, in order to prevent and treat metabolic diseases.

1.3.

What is a metabolic disease?

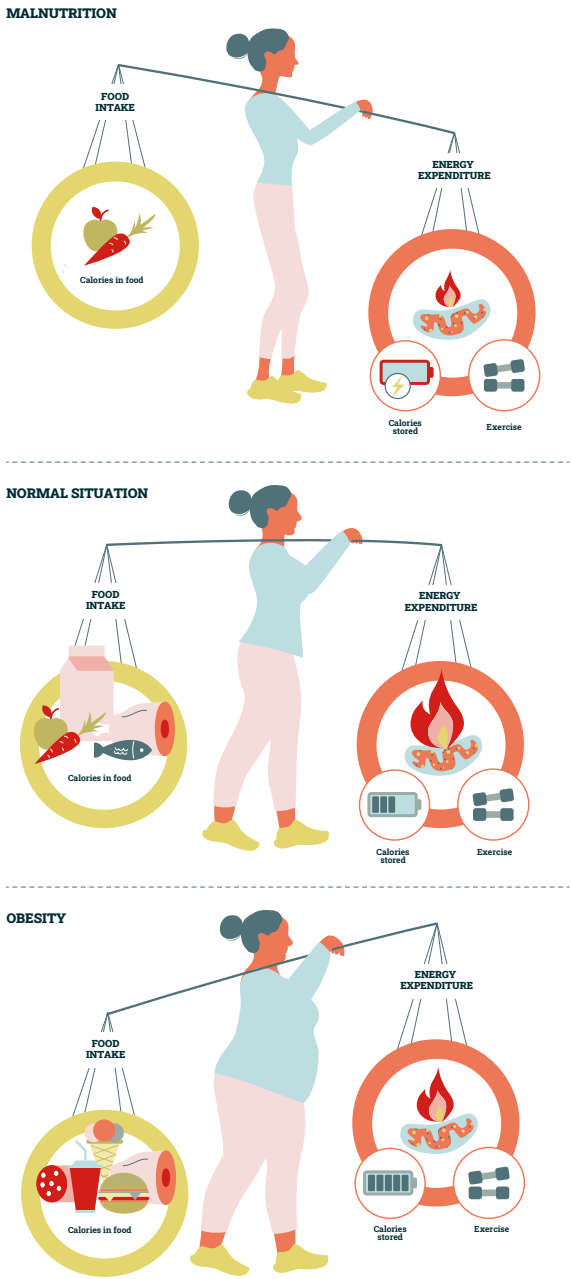
A metabolic disease is defined as any disorder that affects the body's metabolism and its ability to extract, use and store nutrients. Metabolic diseases therefore cover a broad spectrum and pathological scope. They range from rare genetic diseases, e.g., those that cause failure in the production, degradation or excretion of a metabolite, to pathologies resulting from inadequate nutrition.

Metabolic diseases are closely associated with disorders in the body's energy balance. As a whole, the amount of energy available in our body is a balance between the intake and consumption (expenditure) of nutrients, and a balance is necessary for our body to remain healthy. A deficit in intake can lead to a state of malnutrition, while an excess can cause overweight and obesity, leading to the development of metabolic diseases. Energy expenditure is dependent on factors such as genetics, age, and the physical activity of the person.

What are metabolites?

Metabolites are small molecules that are important for energy-producing chemical reactions and for regenerating cellular components that become damaged over time.

Figure 2 Illustration of the energy balance in a shortage (malnutrition), normal and excess (obesity) situation



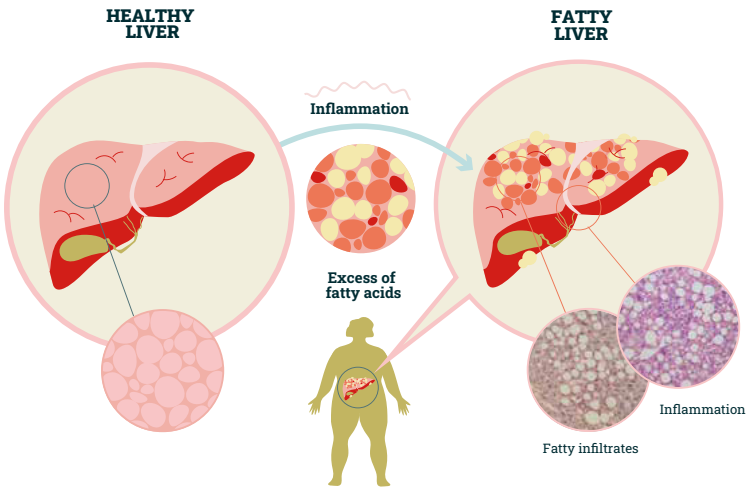
1.4.

Obesity

OBESITY is nowadays considered a chronic disease characterised by an excessive accumulation of fat that is detrimental to health. Obesity increases the risk of diabetes, cardiovascular disease and fatty liver disease.

Fatty liver disease is a pathology caused by the excessive accumulation of lipids in liver cells that inflames the tissue and can cause fibrosis and even progress to cirrhosis or cancer. Currently, the most reliable method for diagnosis and stratification of patients with this liver disease is biopsy, a highly invasive technique. The first treatment has only just been approved (in 2024), reflecting the severe lack of therapies for this disease.

Figure 3 Illustration of the progression and characteristics of fatty liver



Microscopy images from the laboratory of Dr. Ángela Martínez Valverde (IIBM, CSIC)

Obesity is also associated with the development of tumours, autoimmune diseases, poor immune response to infections, acute and chronic renal failure, pancreatitis, biliary diseases, polycystic ovary syndrome and neurological diseases such as bipolar disorder. Taken together, obesity-associated metabolic disorders account for approximately a 50% increased risk of premature death.

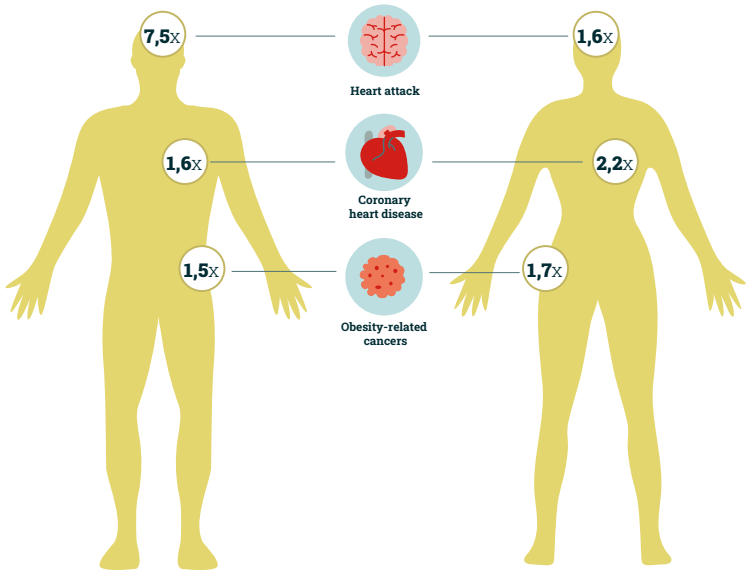
The diagnosis of overweight and obesity is reached by calculating the body mass index (BMI), which is obtained by dividing the value of body weight (in kilos) by height (in metres) squared. The World Health Organisation defines overweight, for the adult population, as a BMI equal to or greater than 25 and obesity as a BMI equal to or greater than 30. Weight gain is associated with an increased risk of premature death in middle-aged adults (21-44 years) of both sexes, although the risk of diabetes and cardiovascular disease due to weight gain increases unequally in men and women.

The link between obesity and metabolic disease has led to the coining of the concept of metabolic syndrome, which is defined by the presence of at least three of the following metabolic disorders: accumulation of visceral fat, increased blood cholesterol (hypercholesterolaemia) and triglycerides (hyperlipaemia), increased blood glucose (hyperglycaemia) and increased blood pressure (hypertension). Metabolic syndrome is a major public health problem, as it is associated with a two- to three-fold increase in the risk of type 2 diabetes and cardiovascular disease. Premature morbidity and mortality due to diabetes and cardiovascular disease are beyond the capacity of health budgets in many countries.

What is the difference between subcutaneous fat and visceral fat?

Fat that accumulates under the skin is called subcutaneous adipose tissue. Fat that accumulates around the internal organs is called adipose tissue or visceral fat. The accumulation of visceral fat is pathological because it secretes substances that alter the function of various organs, such as the liver, pancreas and heart, which promotes the development of metabolic diseases.

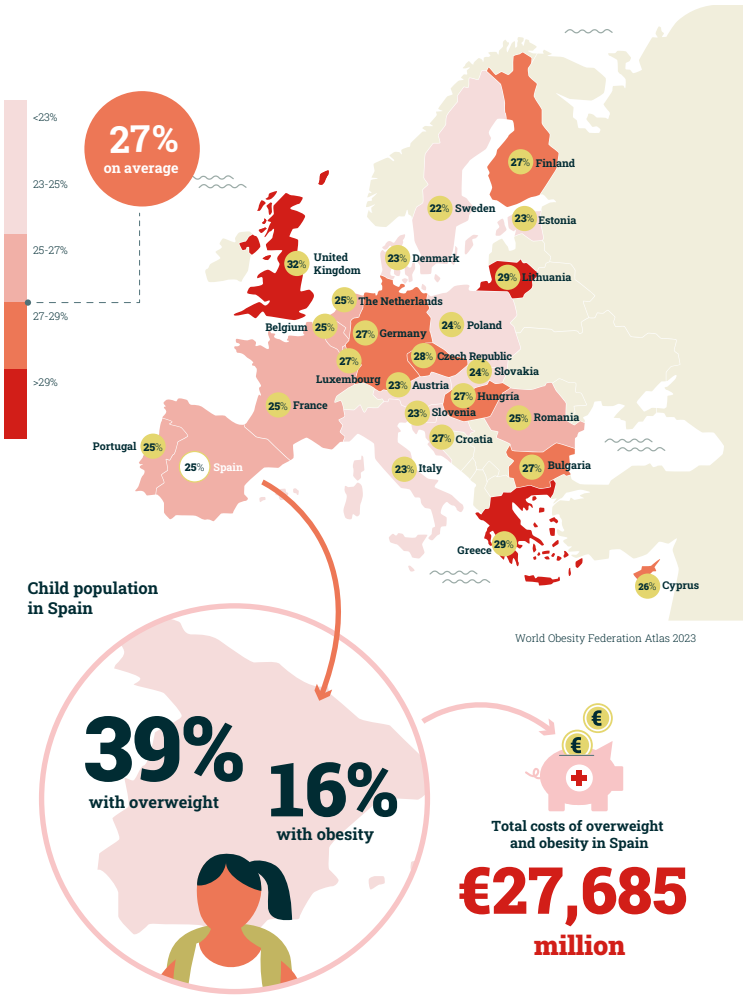
Figure 4 Associated risk of premature death (men/women) and associated risk of metabolic diseases (men/women)



Why does obesity matter?

The World Health Organization estimates that there is approximately 43% of adults worldwide with overweight and a 16% with obesity. Of particular concern is the fact that 37 million children worldwide are overweight. In recent decades, obesity has doubled among adults worldwide and quadrupled among adolescents. To these figures we must add the 828 million people suffering from hunger in the world. In 2020 in Spain approximately 25% of the population was obese and this percentage is growing every year by 1.9% in adults and 2.5% in children.

Figure 5 Prevalence of overweight and obesity in Europe and Spain



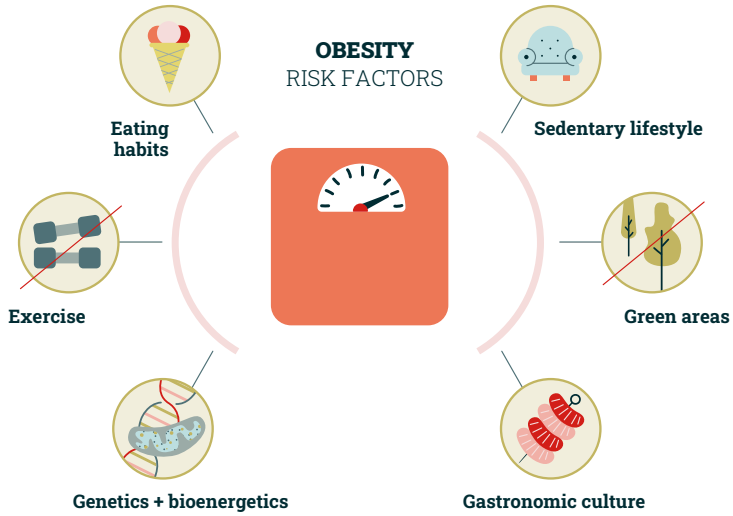
The World Obesity Federation estimates that the global economic impact of overweight and obesity will reach $4.32 trillion per year by 2035 if measures to tackle the epidemic do not improve. This represents almost 3% of global gross domestic product (GDP), comparable only to the impact of COVID-19 in 2020. In Spain, the costs related to obesity and overweight amounted to more than €27 billion in 2021 and are expected to continue to rise until 2060, when they will reach 2.4% of Spanish GDP.

Genetic risk factors

In most cases, obesity has multiple causes, including psychosocial factors and genetics. Individual genetic variants can modify nutritional preferences, frequency of intake and motivation for physical activity, among many other factors that may favour the development of overweight, as well as the subsequent development of metabolic diseases. It has been estimated that the contribution of our genetics to the development of metabolic pathologies accounts for around 30% of the total risk.

It should be noted that only 6% of cases of severe obesity are due to a genetic disease as such. In the remaining cases, the genetic risk of overweight, obesity and the development of metabolic diseases is simply associated with gene variants that are perfectly functional (not pathological), but which in a given context increase our metabolic risk. That is, the same gene variant may be protective in some circumstances and increase the risk in others.

Figure 6 Obesity risk factors



Non-genetic risk factors

Lifestyle, poor diet and lack of physical exercise are the main non-genetic risk factors for the development of obesity. Today's lifestyle has reduced the time spent shopping, cooking and eating healthy foods. Fibre intake has been reduced, consumption of refined sugars, simple carbohydrates and proteins has increased, all associated with the consumption of industrially processed foods, while consumption of fresh fruit and vegetables has decreased. These are all factors that contribute to the development of obesity and metabolic disease. In Spain we are far from meeting the target set by the EU's Farm to Fork strategy, which seeks to "promote sustainable food consumption" to encourage "the transition to healthy and sustainable diets".

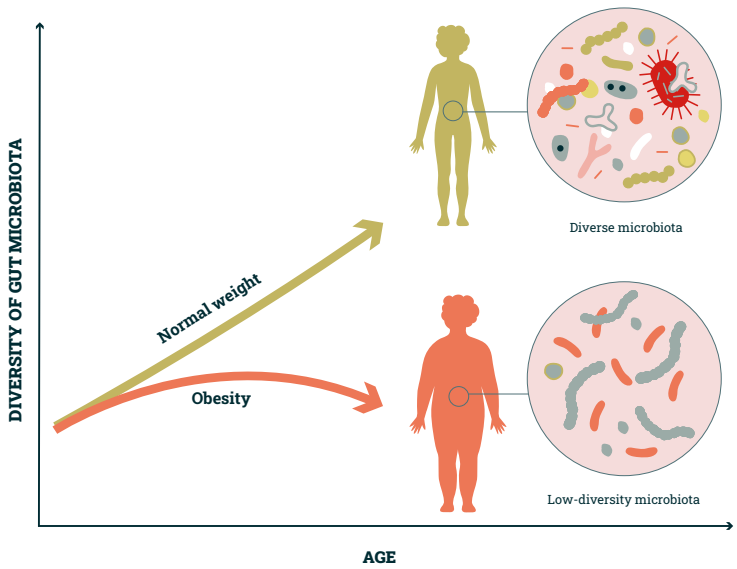
Unhealthy diets lead to alterations in the composition of the gut microbiota, which is the set of microorganisms that inhabit the digestive tract, and the functions of its genome (microbiome), known as dysbiosis. There is a link between dysbiosis and the development of obesity and associated metabolic diseases. In general, individuals with a normal weight have a more diverse gut microbiota in terms of bacterial species than individuals with overweight or obesity.

Gut microbiota

Set of micro-organisms that inhabit our intestine and which includes bacteria, fungi and viruses. They form an ecosystem whose alteration is associated with pathological situations, such as metabolic diseases.

Unbalanced diets (high in calories, saturated fats and simple carbohydrates) reduce the amount of health-promoting bacteria and increase the amount of harmful bacteria that contribute to inflammation and alter the permeability of the intestinal barrier. These alterations allow bacterial components to pass from the gut into the bloodstream, which will spread inflammation to different organs. Blood and other organs should be free of these bacterial components as their presence in these areas results in general (systemic) low-grade inflammation. This inflammation reduces the ability of subcutaneous adipose tissue to store fat and leads to resistance to insulin actions that can result in hyperglycaemia and type 2 diabetes. As a consequence, nutritional interventions that modulate or restore the configuration of a healthy microbiome, such as fibre-rich diets, are being considered as part of the strategies needed for the prevention and treatment of metabolic diseases.

Figure 7 Gut microbiota diversity and its relationship with obesity



Sedentary lifestyles are another risk factor for obesity. The World Health Organisation recommends at least 150 minutes per week of moderate-intensity aerobic physical activity (which requires mitochondrial activity) or 75 minutes of intense physical activity. The level of physical activity of around 35% of the Spanish population aged 15-69 years is low as classified by the World Health Organisation (less than 90 minutes per week). Regular physical activity is essential to prevent and help manage obesity and associated metabolic diseases because it helps increase energy expenditure, activates mitochondrial function and improves overall nutrient management, as well as reducing inflammation.

1.5.

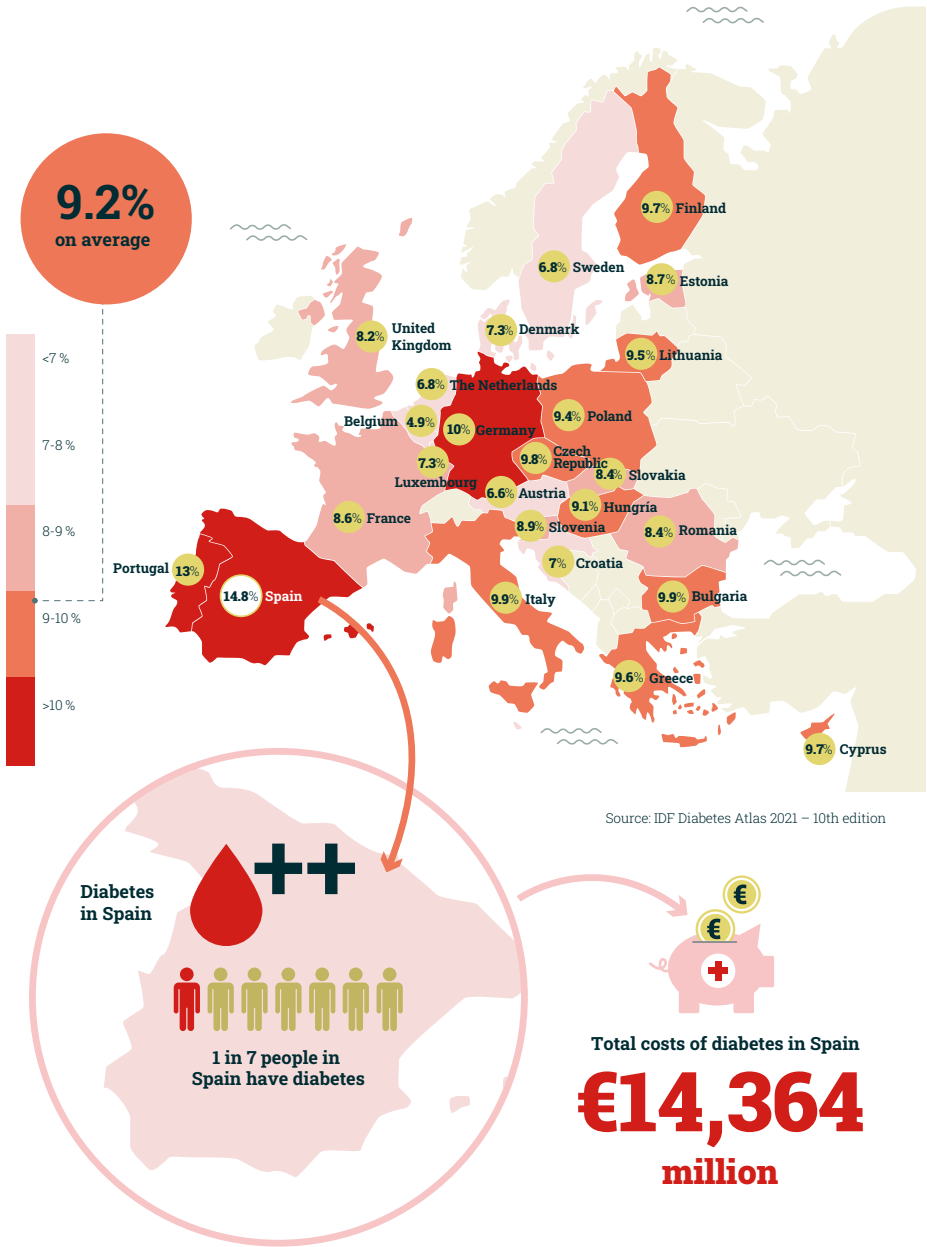
Type 2 diabetes

Diabetes is a chronic disease that occurs when the pancreas fails to secrete enough insulin, the hormone that controls blood glucose levels, or when the body does not respond well to the insulin it produces, known as *insulin resistance*. When this happens, blood glucose becomes abnormally high (hyperglycaemia), a condition that significantly damages blood vessels and eventually leads to malfunction of many organs such as the retina, heart, nervous system, liver and kidney, increasing the risk of developing multiple pathologies. For this reason, we refer to diabetes-related vascular complications to group all these diseases together. In Spain, between 80% and 97% of people with diabetes will develop blindness (retinopathy); between 10% and 21%, kidney failure (nephropathy); and between 60% and 70%, numbness in the limbs (peripheral neuropathy). In addition, people with diabetes have a two to four times higher risk of stroke or myocardial infarction, cognitive impairment or dementia of vascular origin, a type of Alzheimer's disease, and a four times higher risk of developing peripheral vascular disease with a risk of lower limb amputation.

Currently, some 540 million people in the world are living with diabetes, representing approximately 10.5% of the total population. The International Diabetes Federation estimates that by 2045, one in eight adults, about 783 million people, will suffer from diabetes. This represents an increase of 46% over current figures.

There are two types of diabetes, type 1 diabetes, which is autoimmune in nature and in which the ability to produce insulin is lost, and type 2 diabetes, which is often associated with obesity. Type 2 diabetes accounts for 90% of all cases of diabetes. In the European Union, its prevalence in adults is 9.2% and in Spain it is currently 14%, which reflects the special relevance of this pathology in our country.

Figure 8 Prevalence of Diabetes in Europe and Spain



Source: IDF Diabetes Atlas 2021 – 10th edition

Why is type 2 diabetes important?

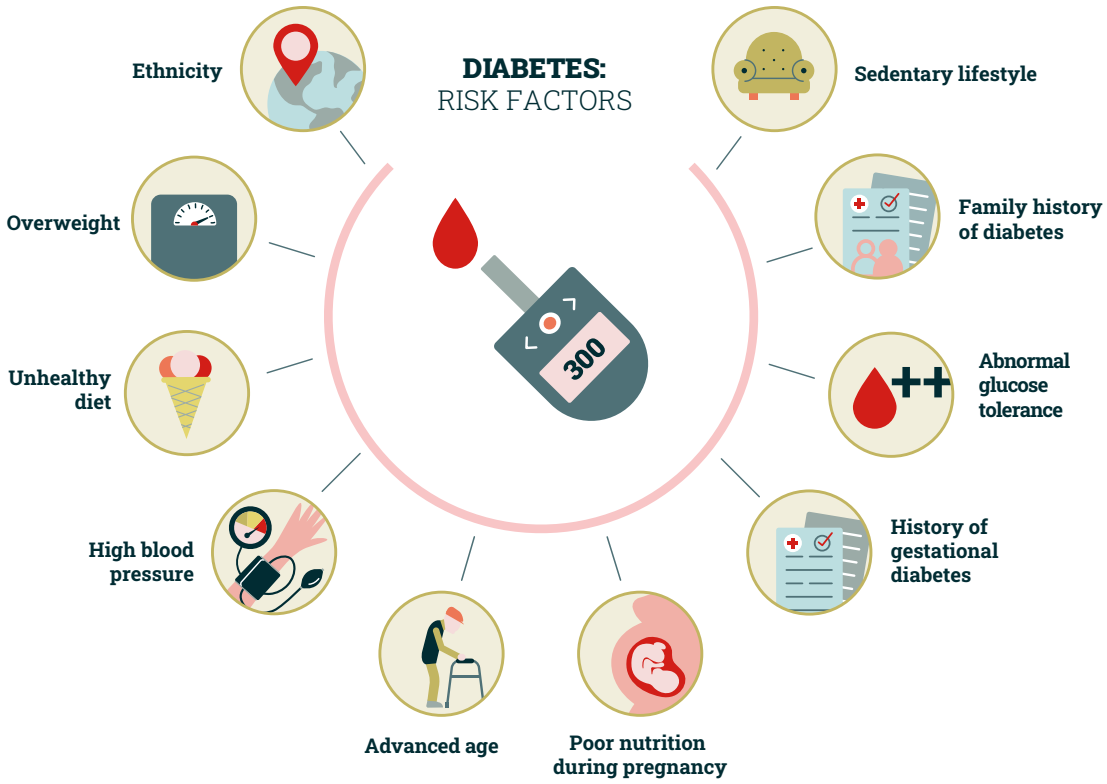
According to the International Diabetes Federation, the total health expenditure related to diabetes in adults globally was around 850 billion euros in 2021, with an estimated upward trend of 2% year-on-year. In Spain, the current healthcare cost per person per year is around €2,800, with a 3% year-on-year rate of increase. According to the Spanish Diabetes Society, 15% of this health expenditure is spent on hypoglycaemic drugs, 24% on hypotensive and lipid-lowering drugs, and the remaining 61% on hospitalisation and primary care costs. Overall, the estimated global cost of diabetes in Spain exceeds 14 billion euros per year. Therefore, proper control of diabetes is essential to prevent the development of complications. According to the Spanish Diabetes Federation, the health expenditure of a patient with good glycaemic control is three times lower than that of a patient without it.

In 2020, an estimated 4.2 million adults died from diabetes and its complications. Diabetes is associated with 11.3% of all adult deaths globally, and affects more women (2.3 million) than men (1.9 million). In Spain in 2021, nearly 25,000 people died from diabetes. In addition to health expenditure, premature death and disability caused by diabetes has a strong economic impact known as the indirect cost of diabetes, which is three times higher than the direct health cost. In the United States, it is estimated that premature deaths from diabetes generate a loss of 19.9 billion dollars per year and a total of 90 billion dollars are lost indirectly. Spain ranks second in the European Union in terms of the number of patients with diabetes, second only to Germany, and therefore has the highest indirect costs associated with it. This expenditure is 50% related to lost working hours and the remaining 50% to early retirement and associated social costs. Permanent disability is mainly due to loss of visual acuity and cardiovascular problems.

Risk factors

The main factors contributing to the increase in the overall prevalence of type 2 diabetes are overweight, obesity, low physical activity, pollutants and other environmental stressors, and an ageing population.

Figure 9 Diabetes risk factors



16.

Cardiovascular diseases

Cardiovascular diseases are a group of pathologies related to the heart and blood vessels. There are three main groups, depending on whether small blood vessels, large blood vessels or the heart are affected. When small vessels are damaged, the blood supply to the tissues is reduced, leading to the development of diseases such as vascular dementia (a type of Alzheimer's disease) and retinal degeneration, which leads to blindness. When large vessels, such as the aorta, are affected, hypertension and atherosclerosis, for example, and when the heart is affected, heart rhythm disorders (arrhythmias), for example, occur.

Atherosclerosis is a pathology that affects the arteries, which appear thickened and stiff. In this context, atheroma plaque develops, an accumulation of oxidised lipids and inflammatory cells in the wall of the arteries, which in advanced stages of the disease accumulates calcium. This calcium causes the plaque to harden and increase in size, causing obstruction of blood flow. If the atheroma plaque ruptures, the fragments released into the bloodstream can cause thrombus formation. Atherosclerosis is therefore a key element in heart attack and stroke. Atherosclerosis occurs frequently in subjects with metabolic syndrome. In this context, the presence of high blood cholesterol levels, which accumulate in plaque, as well as the generalised inflammation associated with obesity become important risk factors.

The development of cardiovascular disease is strongly linked to impaired mitochondrial function. Obesity reduces the activity of mitochondria and their protective role in cell function. In addition, hyperglycaemia and hyperlipidaemia are harmful to mitochondria, which can become irreversibly damaged. In the heart, mitochondrial damage causes the heart muscle to weaken and respond poorly to the electrical impulses that control the heartbeat. Loss of mitochondrial activity in the blood vessels causes poor blood flow, hypertension and plaque formation, among other effects.

Why are cardiovascular diseases important?

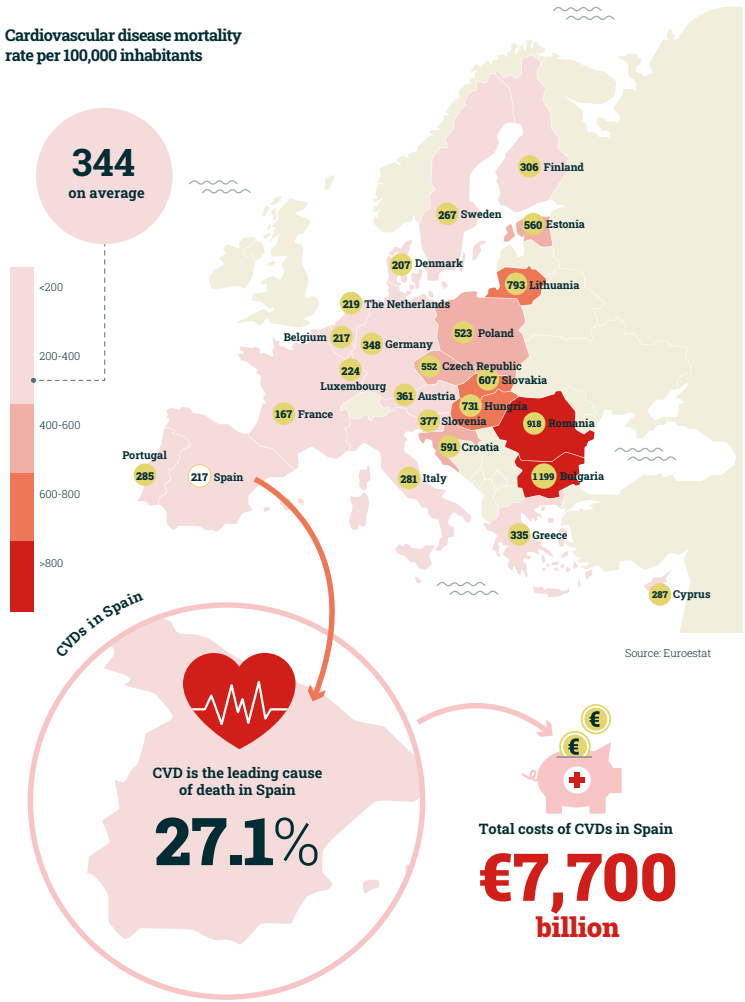
Cardiovascular diseases are the leading cause of death globally and are responsible for approximately 29% of all deaths in women and 33% in men. One third of these deaths affect people under 70 years of age. In Spain, cardiovascular diseases have a prevalence of about 25% of the total population.

According to the European Society of Cardiology, the global health and social cost of cardiovascular diseases is currently 282 billion euros per year, with a health care cost of 11% of total health care expenditure. In Spain, the social and health care cost of cardiovascular diseases has been estimated at €5.35 billion. Adding the indirect costs of these diseases, the total economic cost would be around €7.7 billion per year, with a year-on-year growth of around 3.3%.

Cardiovascular diseases are responsible for 10 million hospitalisations in the European Union per year, 22 per 1000 inhabitants, 14 in Spain. Eight per cent of the five million EU citizens living in institutions are institutionalised because of cardiovascular disease. In addition, home health care accounts for 1229 hours per 1000 inhabitants per year. Approximately 50% of the total healthcare cost is hospital care. Medication accounts for 20% of the expenditure and home and institutional care for 9%. Overall, cardiovascular diseases cost 347 euros per European citizen per year.

In relation to the social cost, the number of hours invested by family members and relatives in caring for the sick would reach 7.5 billion hours per year, which represents an estimated economic cost of 79 billion euros per year in the EU and 7.4 billion euros in Spain. Productivity losses due to death are estimated at 2.8 lost work years per 1000 population. In addition, work days lost due to sick leave account for 1.5 work years lost per 1000 inhabitants. In short, of the total social cost in the European Union, it is estimated that 46% are health care costs; 9% are social-health care costs; 28% derive from unpaid care of patients' relatives and friends; and 17% from loss of production. This represents a cost of €630 per European citizen per year.

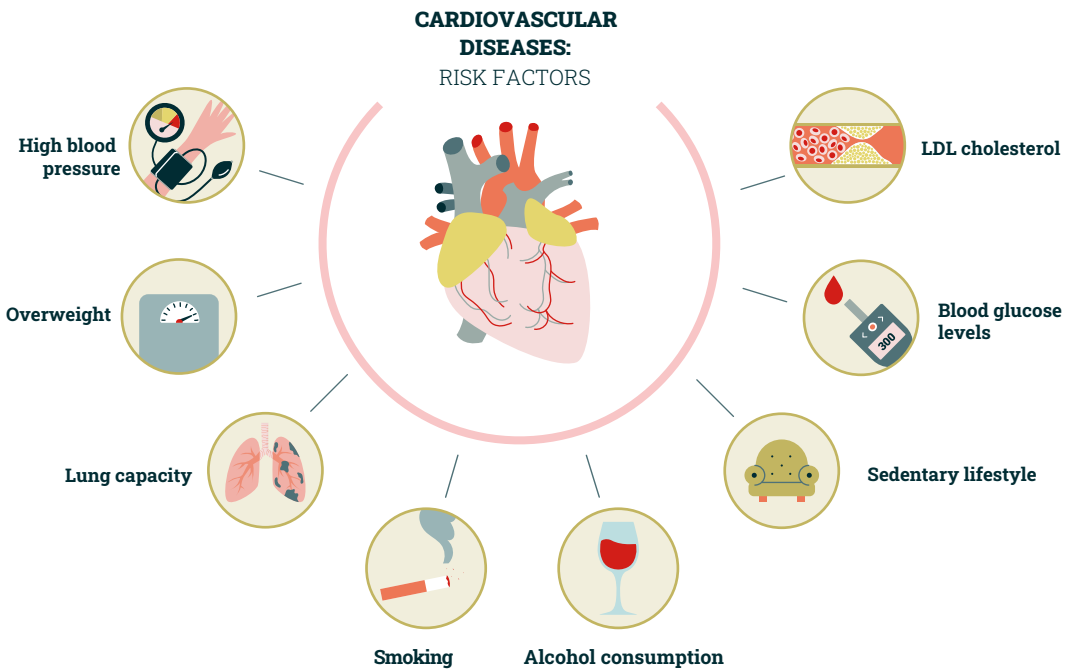
Figure 10 Mortality from cardiovascular diseases in Spain and Europe



Risk factors

The main risk factors for heart disease and cardiovascular events, such as heart attack and stroke, are lifestyle-related: unhealthy diets, low physical activity, smoking and alcohol consumption, among others.

Figure 11 Cardiovascular disease risk factors



two

CSIC's Contribution in the Area of Metabolic Diseases

2.1.

The problem of obesity: breaking new ground in diagnosis and treatment

The problem of non-alcoholic fatty liver disease

Further research is currently needed to expand the molecular and cellular bases that determine the origin and progression of non-alcoholic fatty liver disease. The CSIC is conducting research both from the perspective of finding reliable biomarkers for early diagnosis and disease progression, as well as in the search for treatments for the disease. Using sophisticated lipidomics techniques, CSIC researchers are trying to decipher how toxic lipids cause inflammation and increased insulin resistance in the liver. These studies have determined that hepatocytes release small vesicles containing toxic lipids into the extracellular space, promoting the transport and dissemination of toxic lipids between liver cells. In this way, hepatocyte-secreted vesicles carrying toxic lipids cause inflammation and a decrease in the liver's responsiveness to insulin. The generation of this new knowledge has led to the identification of a novel strategy to attenuate inflammation mediated by toxic lipid-containing vesicles, which would favour an increase in the liver's responsiveness to insulin. This strategy could be used to develop new drugs. Furthermore, the isolation and identification of these vesicles could also be useful for finding biomarkers of the disease.

Inflammation and obesity

Obesity is characterised by an excessive increase in the amount of lipids stored in the body. The CSIC uses complex analytical techniques based on mass spectrometry to identify and characterise the type of lipids present in subjects with obesity. The accumulation of certain lipids causes inflammation, while others act in the opposite way, i.e., they are anti-inflammatory. Research at the CSIC has identified the molecular and cellular mechanisms by which inflammatory lipids can alter cell metabolism, favouring the development of diabetes and cardiovascular disease in subjects with obesity. It also investigates how anti-inflammatory lipids, which promote healthy cellular metabolism, help prevent or mitigate the effects of obesity on the development of diabetes and cardiovascular disease.

The CSIC is currently working intensively to understand how inflammation in individuals with obesity can cause the onset or aggravation of type 2 diabetes and cardiovascular disease, with the aim of providing information for the prevention and treatment of these metabolic diseases.

Deciphering the role of mitochondria in the aetiology of obesity

The CSIC is providing key information to understand the effects of environmental stressors on the energy management of mitochondria in each organ in cases of unhealthy diets and exposure to chemicals and additives, among other stressors. Many of these environmental stressors can accumulate and act preferentially on certain organs. Thus, damage to mitochondria in a single organ is enough to have deleterious effects on an individual's health and be sufficient to cause metabolic disease. Contrarywise, inducing a benefit in the mitochondria of one organ can be transmitted to other tissues.

Mitochondrial malfunction in certain organs may also result from defects in mitochondrial quality control: the process that detects and marks malfunctioning mitochondria in order to repair them or, if the damage is irreparable, to remove them and replace them with new mitochondria. The CSIC is actively investigating whether there are defects in the mechanisms that identify, separate and remove damaged mitochondria and how interaction with other cellular components affects this process. Research also addresses whether there is retention of dysfunctional mitochondria that transmit damage to healthy mitochondria and whether there are failures in the machinery for the removal and recycling of damaged mitochondria. In this regard, very novel projects are underway to define the effects of mitochondrial cholesterol accumulation on the processes of cleavage and removal of damaged mitochondria. Taken together, this knowledge generated at the CSIC will report new strategies to achieve optimal mitochondrial function and improve the health of individuals with metabolic diseases.

Natural bioactive compounds as adjuvant solutions to obesity

One of the approaches used to prevent or delay the onset of obesity is to introduce changes in dietary habits. Recently, natural compounds abundant in seeds, vegetables and fruits have attracted considerable interest due to their safety and their potential ability to act as chemopreventive agents against obesity.

The CSIC is researching the beneficial properties of flavonoids, metabolites present in fruits, vegetables and seeds, as well as in their by-products, such as cocoa, coffee, tea, soya and red wine. Studies have found that flavonoids interact directly with cellular proteins and receptors that are part of the cellular machinery that regulates insulin action, anti-inflammatory response and antioxidant capacity. All these biological processes, when activated, have beneficial effects on metabolic diseases.

The CSIC also develops strategies to optimise food cultivation conditions, as well as industrial processing conditions, to increase the concentration and preserve the functions of beneficial bioactive compounds that can prevent and mitigate metabolic diseases.

Microbiota as a tool in the prevention and treatment of obesity and associated metabolic diseases

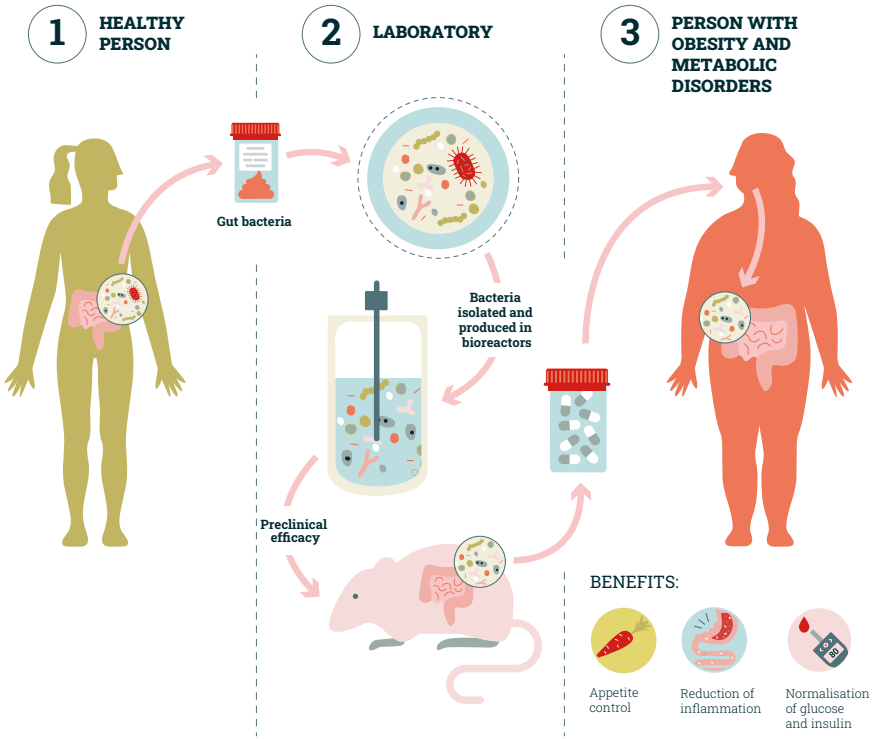
The CSIC is investigating whether the characteristics of the gut microbiota and its functions, together with lifestyle (diet, physical activity, stress, etc.), determine our greater or lesser vulnerability to developing obesity, which may help in the early detection of risk and in prevention. The CSIC is also assessing whether the particular characteristics of our microbiota are responsible for the different efficacy of diets and anti-obesity drugs, in order to recommend the most appropriate ones for each person and improve their efficacy, as well as the design of drugs.

Also being assessed is what role gut bacteria from healthy individuals can play in combating the adverse effects of high-calorie diets on metabolism, both on their own and in cooperation with other bacteria and dietary components. In experimental models, the CSIC has identified bacteria and metabolites (short-chain fatty acids, bile acids or indoles) generated by them from the diet (fibres, polyphenols), which can attenuate obesity-associated inflammation, strengthen intestinal barrier function, glucose intolerance and insulin resistance. CSIC researchers have also identified intestinal bacteria and metabolites that contribute to the synthesis of enteroendocrine hormones and the transmission of their signals from the gut to the brain, which helps control the sensation of hunger and satiety and energy metabolism in peripheral organs such as the liver.

CSIC scientists are also investigating how the temporal pattern (when we eat) and the feeding pattern (what we eat) can modulate the functionality of the microbiota and the generation of satiety or hunger signals, in order to make more precise dietary recommendations.

The CSIC also evaluates how additives and chemical residues (endocrine disruptors) present in the diet could damage the gut microbiota and its functions on our health and, on the other hand, how the metabolic activity of the gut microbiota could reduce or increase the toxicity of chemical compounds.

Figure 12 The microbiota as a tool in the prevention and treatment of obesity



22.

Type 2 diabetes: molecular and cellular basis and the development of new drugs

Ever since Frederick Banting and his colleagues identified insulin as a key hormone for the treatment of diabetes in 1921, the scientific community has focused on understanding how this hormone is produced, acts and is eliminated in the human body.

One of the problems with type 1 diabetes is that from a very early age our immune system attacks and destroys the cells that produce insulin (beta-pancreatic cells), making it necessary to replace them with new cells. One therapeutic option for these patients is beta-pancreatic cell transplantation, but the shortage of organ donors is a major limitation to this approach. Thus, alternative sources of insulin-producing cells need to be developed. CSIC scientists are investigating how to obtain these cells from stem cells. To this end, specialised molecules (called transcription factors) are being identified that are responsible for governing the processes that transform a stem cell into an insulin-producing cell. In parallel, the conditions under which these transcriptional factors are turned on or off are being investigated in order to map the sequence of events that determines the formation of an insulin-producing cell. The ultimate goal is to obtain insulin-producing cells in large quantities from stem cells.

With age, people with type 2 diabetes produce less insulin and their ability to regulate blood glucose levels decreases. The CSIC is investigating how insulin is produced and secreted in order to develop new drugs that enhance the ability to produce this hormone as we age. On the other hand, 50%-75% of the insulin produced is rapidly eliminated by the liver before it can perform its functions. The CSIC is attempting to understand how this hormone is eliminated in our bodies using transgenic animal models, in order to develop pharmacological interventions to increase the availability of insulin in people with type 2 diabetes. Finally, research is also underway on how insulin acts on cells through complex intracellular signalling pathways that ultimately regulate the processes of glucose uptake and utilisation, as well as fat synthesis. This research may facilitate the discovery of new drug targets to increase the efficacy of the hormone as a therapeutic alternative for the treatment of diabetes.

Deciphering the role of mitochondria in type 2 diabetes

Evidence shows that mitochondria are closely linked to the development of type 2 diabetes. The CSIC is investigating how they work and the changes that occur in the mitochondria of people with diabetes. Thus, high-calorie diets and obesity cause changes in the mitochondrial components of insulin-producing cells, altering some of their specific functions (such as the production of reactive oxygen species) that may increase the risk of developing insulin resistance. Since these alterations in the mitochondria of insulin-producing cells may promote pre-diabetes in healthy individuals, these studies could be useful in developing new strategies for manipulating mitochondrial function to prevent the disease.

Paradoxically, reactive oxygen species produced by mitochondria can play a beneficial role, as they are used as signals that monitor mitochondrial function, activate protection and repair systems, and promote the generation of new mitochondria. What makes the difference between the benefit and harm of reactive oxygen species is the dose, where and when they are generated. CSIC researchers are investigating the beneficial or harmful effects of antioxidant supplementation on the production of mitochondrial reactive oxygen species as possible treatments for diabetes.

Finally, mitochondria have a great capacity to move within a cell to contact other organelles, as well as to fuse and fission. The physical contacts of mitochondria with other cell components and the processes of mitochondrial fusion and fission are key events for mitochondrial quality control. The CSIC is analysing the effects of manipulating fusion and fission between mitochondria and mitochondrial contacts with other organelles on the development of diabetes and other metabolic diseases.

The search for new drugs to prevent and treat type 2 diabetes

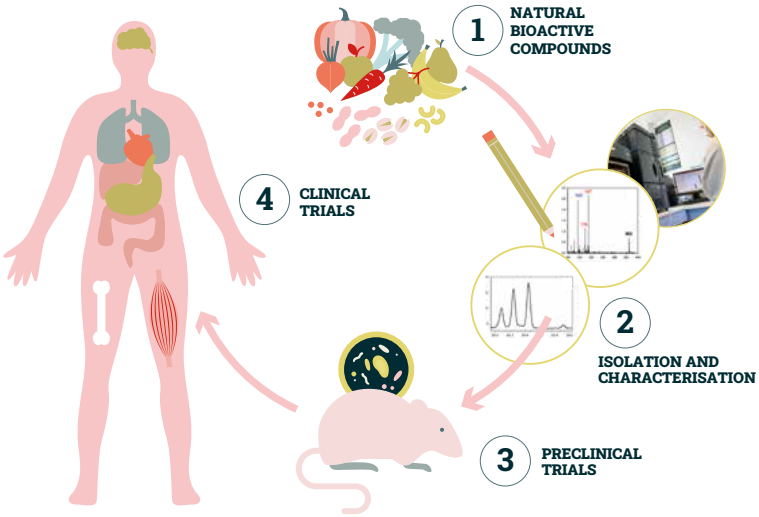
The CSIC is searching for new drugs that increase insulin production (secretagogues) and those that enhance hormone action (sensitisers) in natural compounds present in algae and marine corals. The first phase consists of the isolation, characterisation and identification of unknown compounds. In the second phase, compounds that are toxic to cells are screened out and those that are non-toxic are selected. In the third phase, compounds with potential pharmacological potential for the treatment of diabetes are identified. Cell lines and cell cultures from diabetic animals are used for this purpose. Finally, the most promising compounds are tested in diabetic animal models. In other cases, the search for new drugs has been based on prior knowledge of molecules found in our bodies. Thus, CSIC researchers have chemically synthesised a protein that is produced exclusively during pregnancy and that has the capacity to increase insulin secretion in preclinical models of diabetes, alleviating hyperglycaemia. This new knowledge generated by the CSIC aims to achieve safer, more effective and cheaper drugs.

The CSIC, together with other institutions, has participated in clinical trials to demonstrate the preventive effect against type 2 diabetes of oleanolic acid isolated from olive leaves. This research has revealed the therapeutic usefulness of this compound as an adjuvant to metformin, the first-line drug used in the treatment of people with diabetes.

Finally, the CSIC not only seeks new anti-diabetic drugs; it is also interested in understanding why, in recent years, an increase in the incidence of type 2 diabetes has been described in patients receiving pharmacological treatment in the context of other diseases. This is the case of schizophrenia patients receiving chronic treatment with second-generation antipsychotics (such

as olanzapine or aripiprazole), where the risk of developing diabetes may be four times higher than in the healthy population. CSIC researchers have elucidated some of the metabolic alterations associated with treatment with these antipsychotics, such as weight gain and beta-pancreatic cell dysfunction, leading to hyperglycaemia and an increased risk of diabetes. Understanding the adverse effects of chronic antipsychotic treatment is of paramount importance to prevent the increase of diabetes in the population.

Figure 13 Some of the strategies developed at the CSIC for the treatment of metabolic diseases



Spectral plots from the laboratory of Dr. Jesús Balsinde (IBGM, CSIC).

23.

Cardiovascular diseases: identification of determinants and development of new therapeutic targets

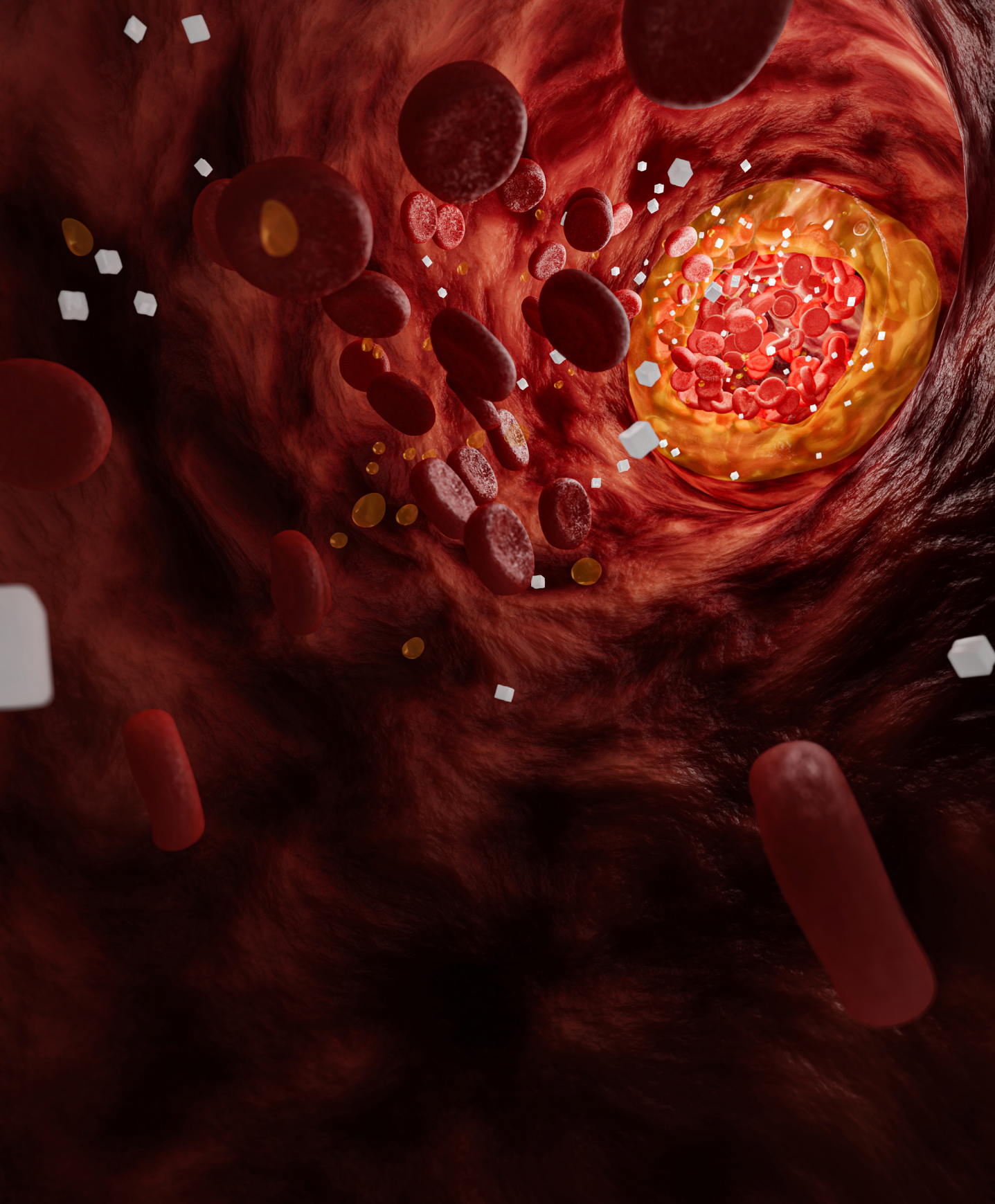
Atherosclerosis in cardiovascular disease

The CSIC studies the processes of atheroma plaque formation that cause thickening and stiffening of the arteries. Macrophages are specialised cells of our immune system that contribute to the generation of plaque and the clogging of arteries. The CSIC is investigating how the production and accumulation of lipids in these macrophages is regulated, to establish if manipulation of these lipids could mitigate plaque formation.

Vessel remodelling in cardiovascular disease

The optimal distribution of nutrients and oxygen is a function carried out by blood vessels (arteries and veins), which must continuously adapt to the changing needs of tissues. CSIC research addresses the cellular and molecular bases that govern the remodelling of blood vessels, both in terms of the synthesis and assembly of the components of the matrix that surrounds these vessels, and of the actions of proteins that reside in this extracellular matrix. These proteins are called metalloproteinases and have the ability to determine integrity and to combat foreign invaders such as bacteria.

Pathological remodelling of the blood vessel wall is a critical process in the development of atherosclerosis, hypertension and aneurysms. CSIC researchers have focused on discovering new genes capable of mediating this remodelling. The result has been the identification of new therapeutic targets for cardiovascular diseases.



Inflammation and cardiovascular disease

The CSIC is conducting research on the involvement of metabolism in the resolution of inflammatory processes associated with cardiovascular disease. For example, our researchers are attempting to understand the relationship between the bioenergetics of macrophages located in the atheroma plaque and the ability to reduce inflammation in the plaque. These studies are developing metabolic maps of immune cells that may guide new therapeutic interventions aimed at preventing atheroma plaque formation. These interventions could combat the ischaemia and heart failure that are characteristic of cardiovascular disease.

CSIC research has also determined that inflammation alters cell metabolism to cause calcification of the cardiovascular system. This knowledge has enabled the search for therapies based on the manipulation of metabolic intermediates involved in calcification. In addition, the potential treatment of these diseases is being investigated through new therapeutic uses of drugs currently used in patients with autoimmune diseases.

Finally, endothelial cells in blood vessels form a selective barrier that controls the passage of cells and solutes between the blood and the parenchyma (the tissue of glandular organs). CSIC researchers study how inflammatory mediators alter the adherens junctions between endothelial cells and cause alterations in endothelial barrier function.

The importance of mitochondria in cardiovascular disease

Hypercholesterolaemia is a risk factor for cardiovascular disease. For example, cholesterol and other lipids can directly damage the mitochondria of cardiomyocytes (the cells of the heart muscle). This damage to cardiomyocyte mitochondria differs from that caused by ischaemic events (when blood flow to the heart is stopped for a short period of time). An immunotherapy is being developed at CSIC to decrease cholesterol entry into the cardiomyocyte to improve cardiovascular function.

Fat accumulation in vascular tissue is associated with the development of fibrosis. Fibrosis is the replacement of healthy tissue with scar tissue, which causes the tissue or organ not to function properly. At the CSIC, scientists are determining how an excess of reactive oxygen species, some of which are lipidic in nature, can alter blood vessels and induce this fibrosis. Simultaneously, they are investigating ways to make the mitochondria oxidise these excess lipids, produce fewer reactive oxygen species and stop the fibrosis.

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Conclusions and Recommendations

Conclusions

Metabolic diseases have a major social, health and economic impact and are one of the greatest challenges we face in the 21st century.

Metabolic diseases are the result of a complex interaction between the widespread adoption of unhealthy lifestyles in societies with poorly planned urban development, the exposure of the population to environmental stressors and the individual's genetic predisposition. Therefore, the onset of these diseases in the individual does not always follow the same pattern and there is no single approach to curb and control the development of metabolic diseases.

Comprehensively addressing the current challenges posed by these diseases requires commitments between political and social actors, the health sector and the industrial sector. Policies and actions that improve the well-being of individuals and achieve economic sustainability need to be identified and implemented for the prevention and control of metabolic diseases.

The CSIC develops research projects that include the most important emerging challenges caused by metabolic diseases, and aims to become a national and international benchmark.

The science developed at the CSIC is aimed at providing new knowledge on the molecular, cellular and genetic bases of metabolic diseases, as well as their physiopathology and their relationship with environmental risk factors, in order to transfer this knowledge to society and industry through the generation of products, procedures and information.

Recommendations

For policy-makers:

Funding and political and governmental commitment are crucial in the medium and long-term fight against these epidemics of the 21st century. In this sense, it is necessary to establish a broad political consensus (at all political-administrative levels) that allows a sustained increase in public funding over time in strategic lines in the field of metabolic diseases, through the creation of new calls for projects to generate knowledge, public-private collaboration and the attraction and stabilisation of talent.

In terms of training, education and public outreach, curricular itineraries should be promoted at all levels of the national education system that include prevention programmes on the main risk factors for metabolic diseases, nutritional education programmes and information programmes on the consequences of these diseases on our health. These curricular itineraries should be implemented in educational centres (from nursery schools to universities) and should be carried out from an intersectoral and cross-cutting perspective, with the participation of the National Health System mechanisms or services (such as primary care centres), the main social agents and patients' associations.

Health measures related to the prevention, surveillance and control of metabolic diseases should be encouraged and supported. These measures could include, among others, the publication of scientific guidelines on the prevention of these diseases and the development of agreed standards and diagnostic criteria. In the same vein, legislative changes should be encouraged in relation to nutrition labelling of foods, advertising of foods and beverages to children and adolescents, and encouraging access to healthy foods at affordable prices. Together, these legislative measures would help consumers make informed choices about their metabolic health.

The multifactorial nature of metabolic diseases, and the individual predisposition of the subject to suffer from them, require a new approach to the provision of diagnostic and treatment services offered by the National Health System for these diseases. In this regard, it is advisable to promote precision medicine and nutrition, in order to apply the most appropriate diagnostic and therapeutic procedures to those subgroups of the population that share similar characteristics of metabolic diseases. Precision medicine and nutrition are a first step in laying the foundations for personalised medicine and nutrition, in which clinicians should tailor medical and dietary treatments to the preferences and biological characteristics of individual patients, who should be able to participate proactively in the decision-making process regarding their health.

From the point of view of the public policy instruments available and the organisation of research, the Spanish Strategy for Science, Technology and Innovation (EECTI) 2021-2027 is a tool that serves as a reference for drawing up the State Plans for Scientific and Technical Research and Innovation (PEICTI). It would be advisable to include metabolic diseases as strategic lines of national R&D&I within the Health and Food areas.

The creation of networks that promote the complementarity of capacities and the optimisation of existing research resources for the study of metabolic diseases should be encouraged. The Conexiones (CSIC-HUBs) and Interdisciplinary Thematic Platforms (PTIs) on metabolic diseases would be of particular relevance to facilitate synergies between CSIC research groups, as well as with other national and international research centres and universities.

For companies:

Promoting forums for the exchange of information, ideas and solutions aimed at preventing and controlling metabolic diseases. From the point of view of the instruments available at the CSIC, a Cicerón Itinerary focusing on metabolic diseases is an effective tool for bringing CSIC research groups closer to the business sector, foundations, health administrations and patient associations.

Establishing collaborative instruments between the business fabric and scientific institutions that facilitate the creation of start-ups based on disruptive scientific and technological knowledge, which achieve more ambitious goals in the prevention and control of metabolic diseases.

Continuing the commitment to measures taken by the food and beverage processing industry to reformulate and improve the composition of packaged foods and the food supply, in particular with regard to the reduction of added sugars, salt and saturated fats. Include the catering sector in this strategy to improve the quality of food consumed outside the home. In addition, reaching new commitments within the sector by promoting active living, emotional well-being and good sleep habits, which are some of the objectives of the national strategic plans for the *Reduction of Childhood Obesity* (2022-2030).

The chronicity of metabolic diseases requires greater involvement of the pharmaceutical industry in the development of new drugs that provide the greatest benefits at the lowest possible economic cost, as well as a greater focus on prevention. These initiatives will favour the sustainability of the healthcare system and greater availability and access to pharmacological treatments for the population.

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For society:

It is crucial that civil society becomes aware of its role in the prevention and control of its own health, through the generation and strengthening of patient groups (associations, foundations or other collectives), together with strategies aimed at the general population. These organisational structures could be an effective instrument of collaboration with governmental organisations, health entities and scientific bodies in the mission of disseminating, promoting and implementing healthy habits.

To better understand the causes and effects of metabolic diseases, as well as to make progress in their prevention and therapy, there is a need for longitudinal population-based and clinical studies that consider the diversity in lifestyles, environmental stressors, the microbiome and genetic susceptibility of the general population. These actions require the involvement and participation of both the healthy subject and the patient in epidemiological studies and clinical trials.

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List of Centres

CENTRE	WEB PAGE	E-MAIL
Centro Andaluz de Biología del Desarrollo (CABD, CSIC-Junta de Andalucia-UPO)	http://www.cabd.es/	direccion.cabd@csic.es
Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER, CSIC-Junta de Andalucia-Universidad de Sevilla-UPO)	http://www.cabimer.es/	direccion.cabimer@csic.es
Centro de Biología Molecular Severo Ochoa (CBM, CSIC-UAM)	http://www.cbm.csic.es/	direccion.cbm@csic.es
Centro de Edafología y Biología Aplicada del Segura (CEBAS, CSIC)	http://www.cebas.csic.es/	direccion.cebas@csic.es
Centro de Investigaciones Biológicas Margarita Salas (CIB, CSIC)	http://www.cib.csic.es/	direccion.cib@csic.es
Centro Nacional de Biotecnología (CNB, CSIC)	http://www.cnb.csic.es/	direccion.cnb@csic.es
Instituto de Agroquímica y Tecnología de Alimentos (IATA, CSIC)	http://www.iata.csic.es/	direccion.iata@csic.es
Instituto de Biología Funcional y Genómica (IBFG, CSIC-Universidad de Salamanca)	http://ibfg.usal-csic.es/	direccion.ibfg@csic.es
Instituto de Biología Molecular de Barcelona (IBMB, CSIC)	http://www.ibmb.csic.es/	direccion.ibmb@csic.es
Instituto de Biomedicina de Sevilla (IBIS, CSIC-US-Junta de Andalucia-SAS)	http://www.ibis-sevilla.es/	direccion.ibis@csic.es
Instituto de Biomedicina de Valencia (IBV, CSIC)	http://www.ibv.csic.es/	direccion.ibv@csic.es
Instituto de Biomedicina y Genética Molecular de Valladolid (IBGM, CSIC-UVA)	http://www.ibgm.med.uva.es/	direccion.ibgm@csic.es

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Instituto de Ciencia y Tecnología de Alimentos y Nutrición (ICTAN, CSIC)	http://www.ictan.csic.es/	direccion.ictan@csic.es
Instituto de Investigaciones Biomédicas de Barcelona (IIBB, CSIC)	http://www.iibb.csic.es/	direccion.iibb@csic.es
Instituto de Investigaciones Biomédicas Sols-Morreale (IIBM, CSIC-UAM)	http://www.iib.csic.es/	direccion.iibm@csic.es
Instituto de la Grasa (IG, CSIC)	http://www.ig.csic.es/	direccion.ig@csic.es
Instituto de Parasitología y Biomedicina López Neyra (IPBLN, CSIC)	http://www.ipb.csic.es/	direccion.ipbln@csic.es
Instituto de Productos Lácteos de Asturias (IPLA, CSIC)	http://www.ipla.csic.es/	direccion.ipla@csic.es
Instituto de Productos Naturales y Agrobiología (IPNA, CSIC)	http://www.ipna.csic.es/	direccion.ipna@csic.es
Instituto de Química Avanzada de Cataluña (IQAC, CSIC)	http://www.iqac.csic.es/	direccion.iqac@csic.es

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Further Information

WHO website (non-communicable diseases)
https://www.who.int/es/news-room/fact-sheets/detail/noncommunicable-diseases

WHO website (obesity and overweight)
https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight

WHO website (diabetes)
https://www.who.int/es/news-room/fact-sheets/detail/diabetes

WHO website (cardiovascular diseases)
https://www.who.int/es/health-topics/cardiovascular-diseases

10th Edition Diabetes Atlas (International Diabetes Federation)
https://diabetesatlas.org/atlas/tenth-edition/

World Obesity Atlas 2024
https://www.worldobesity.org/news/world-obesity-atlas-2024

Atlas of Cardiology (European Society of Cardiology)
https://www.escardio.org/Research/ESC-Atlas-of-cardiology

Science for Public Policy

Knowledge Transfer Report

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