WHAT IS...?

Sugary foods cause a rapid increase in blood sugar levels

Genetic and environmental factors relating to diabetes

Geneticist Katy Walsh explains how understanding diabetes will help guide global strategies that target the growing burden of this disease

Diabetes mellitus is a metabolic disease that affects around 9% of the global population. It appears to affect some populations more than others. This is thought to be due to both genetic and environmental factors.

Glucose homeostasis is a feedback loop that operates to maintain a blood glucose concentration within a normal range. This is achieved through two hormones: insulin and glucagon. When glucose concentrations are high (for example, after eating), insulin is released from the pancreas. Insulin acts on muscle, fat and the liver, triggering glucose absorption and thus reducing the blood glucose concentration (see Figure 1). When glucose concentrations are low, glucagon is released from the pancreas but acts solely on the liver. Glucagon promotes the breakdown of glycogen into glucose, therefore increasing blood glucose concentrations.

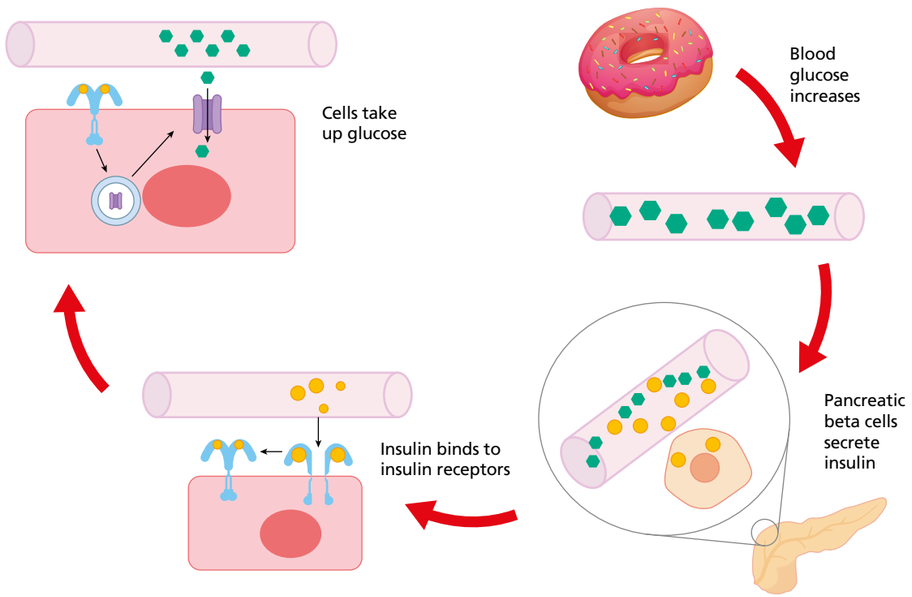


Figure 1 Normal response following a meal. Blood glucose (green) increases, triggering beta cells in the pancreas to secrete insulin (yellow). Insulin travels through the blood and passes through the blood vessel wall in order to bind to insulin receptors (blue) primarily found on muscle, liver and fat cells (pink). This receptor–molecule binding signals for glucose transporters (purple) to migrate from the cytoplasm to the cell surface membrane (via vesicles) and transport glucose into the cell. This lowers the blood glucose, returning to the start of the cycle

Type 1 diabetes is an autoimmune disease that is generally diagnosed during childhood. The body's immune system attacks the pancreatic beta cells that produce insulin, so little or no insulin is produced (see Figure 2). As a result, blood glucose concentrations are high, so regular injections of insulin are needed to prevent hyperglycaemia.

Type 2 diabetes is characterised by insulin resistance. Appropriate levels of insulin are produced, but muscle, adipose and liver tissues are less responsive (see Figure 2). This means less glucose uptake occurs, and blood glucose concentration remains high. While there are drugs that can increase insulin sensitivity, the best treatment for type 2 diabetes is a change in lifestyle. This includes improving diet and increasing exercise.

Diabetes is estimated to affect almost one in ten of the global population, but the percentage varies massively across urbanisation, ethnicity, age, sex and income. Ethnicity and sex suggest a genetic element, while urbanisation and income suggest an environmental contribution. Taking each of these factors into consideration can help explain the **aetiology** of diabetes, but also guide global efforts in tackling the growing demands of the diabetic population.

Genetics

There is no single cause of type 1 diabetes, but several genetic risk factors have been identified. These include alleles for the human leukocyte **antigen** (HLA) complex, a component of the immune system involved in distinguishing the body's own proteins from those of pathogenic origin. Having the risk HLA alleles does not necessarily mean you will develop type 1 diabetes, as environmental triggers are also required. Autoimmune disease triggers include molecular mimicry and sequestered antigens. The former refers to bacteria and viruses with antigens similar to those of pancreatic beta cell antigens, which trigger an immune response that attacks both the pathogen and host. Sequestered antigens refers to pancreatic beta cell antigens being hidden from the immune system but a sudden release or exposure triggers an autoimmune reaction.

If a parent has type 1 diabetes, there is a 5% chance that any of their children will also develop type 1 diabetes. However, if both parents are affected, the chance goes up to 30%.

Specific alleles of genes encoding components of glucose transport and insulin regulation increase the risk of developing type 2 diabetes. But distinguishing between genetic and environmental

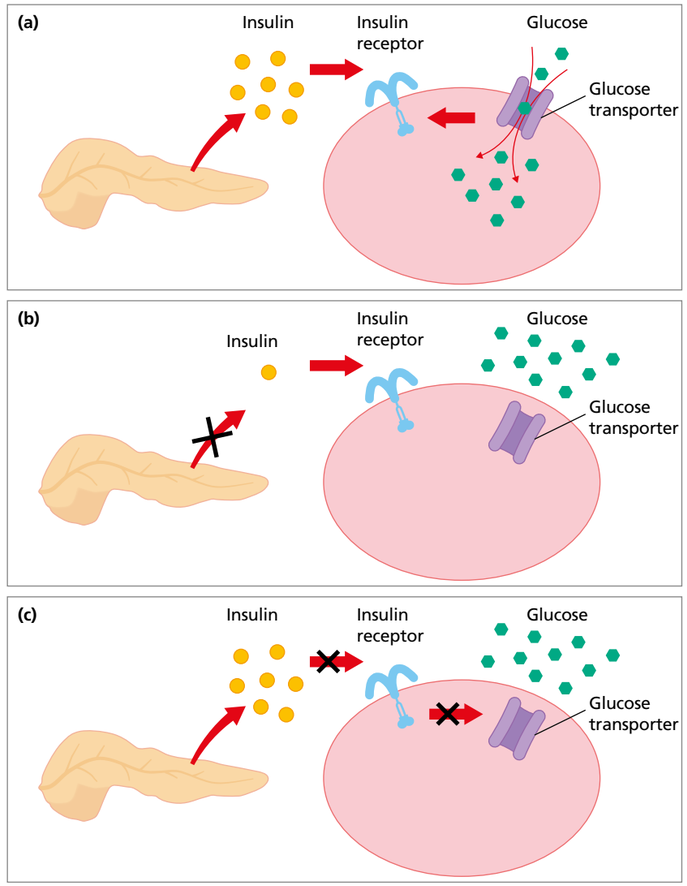
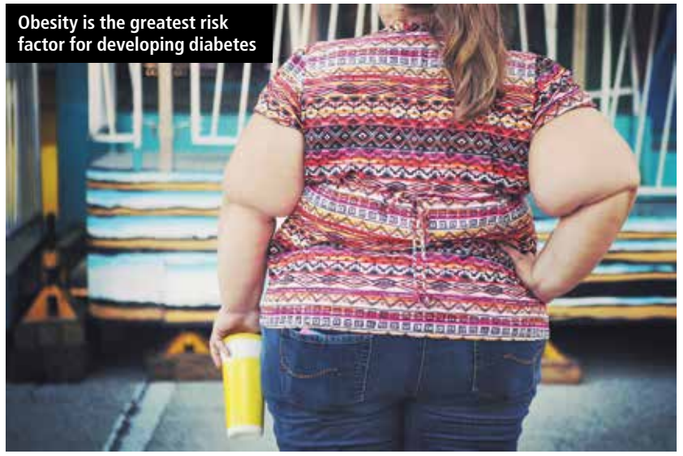


Figure 2 Diagrams summarising insulin action in (a) health and in (b) type 1 and (c) type 2 diabetes


Obesity is the greatest risk factor for developing diabetes

factors is more complex with type 2 diabetes. For example, a genetic predisposition to obesity is not a genetic predisposition to type 2 diabetes, but being obese significantly increases the likelihood of its development.

A rare form of diabetes that does not fit into the type 1 and type 2 categorisation is maturity-onset diabetes of the young (MODY). This accounts for 1–2% of all diabetes cases. It is caused by a single mutation in any one of eleven different genes. Like type 1 diabetes, affected individuals produce no insulin even though their pancreatic beta cells are intact. The mutations that cause MODY are in genes involved in the transcription of insulin, and prevent insulin production or its release from the beta cells. These mutations are autosomal dominant, so offspring of a parent with a MODY mutation have a 50% chance of also inheriting the mutation and thus developing MODY.

Sex-specific diabetes risk

Sex bias is common in many conditions, including immune disorders and cardiovascular disease. Males are more likely to develop type 2 diabetes at a lower **BMI** than females. However, obesity, the biggest risk factor for developing type 2, is more common in females. Data from the World Health Organization (WHO) suggests that males aged 39–60 are significantly more likely to develop type 2 diabetes, whereas over the age of 70 it is women who have a higher chance. Many autoimmune diseases also show a significant bias towards females, but there is very little difference between men and women for type 1 diabetes. A 2019 **meta-analysis** by a research group in Wuhan, China, suggests that women with diabetes have a higher mortality rate than men, but the molecular mechanisms behind this are unknown.

Gestational diabetes can occur in mothers during pregnancy when insulin sensitivity decreases such that hyperglycaemia occurs, much like type 2 diabetes. Gestational diabetes is usually diagnosed in the second trimester of pregnancy and, in general, normal blood sugar concentrations return following birth. However, women who have had gestational diabetes during pregnancy are significantly more likely to develop type 2 diabetes in the future, as are their children. Curiously, the risk of developing gestational diabetes is 4% higher in women carrying a male fetus than female, further highlighting sex differences in diabetes.

Ethnicity

Studies into the association between ethnicity and the development of diabetes have mainly been done in the USA, due to its diverse ethnic population, and high levels of obesity that link to type 2 diabetes. Research conducted by the Centers for Disease Control and Prevention (CDC) showed that African American, Asian and Hispanic American people all have a higher prevalence of type 2 diabetes than white American people, whereas white American people have a higher prevalence of type 1 diabetes.

TERMS EXPLAINED

Aetiology Causes of a disease, including the factors that predispose disease development.

Antigen Molecules on the surface of cells that allow cell–cell and cell–environment recognition.

BMI Body mass index, calculated using mass (kg) divided by height^2 (m^2). A healthy BMI is between 18.5 kg m^{-2} and 24.9 kg m^{-2}.

Meta-analysis A combination of the results of many studies.

On a global scale, the prevalence of diabetes in the Middle East and North Africa is almost three times higher than in sub-Saharan Africa, and almost double that in Europe. Differences in the prevalence between ethnic groups is likely to have both genetic and environmental factors. As the genetics of type 2 diabetes is complex, it is difficult to identify any significant genetic variations that would account for these differences. However, environmental and socio-economic factors including smoking, access to higher levels of education, access to healthcare, availability of medicine and language barriers all contribute to the risk of developing type 2 diabetes.

Globalisation and geography

With rapid development of countries comes a correspondingly quick change in lifestyle for their populations. In the last 40 years, China has undergone massive urbanisation, causing changes from traditional dietary patterns and reduced exercise levels linked to the built-up nature of the new cities. This change in diet leans towards a high fat and high sugar intake, linked with the availability of fast food. As a result, obesity in China has increased rapidly, leading to a significant increase in the prevalence of type 2 diabetes.

Other populations with high availability of junk food, such as the USA, also have high prevalence of type 2 diabetes (see Figure 3). Relating back to ethnicity, Eastern Asian populations, such as China, have a higher risk of developing type 2 diabetes at a lower BMI than European populations. It is increasingly clear that diabetes is more prevalent in urban than rural areas.

While obesity is the greatest risk factor for the development of type 2 diabetes, smoking also presents a significant risk. The mechanisms for this are unclear, but smoking increases insulin resistance. The majority of the world's cigarette production is carried out in China and India, countries that allow mass advertising of tobacco

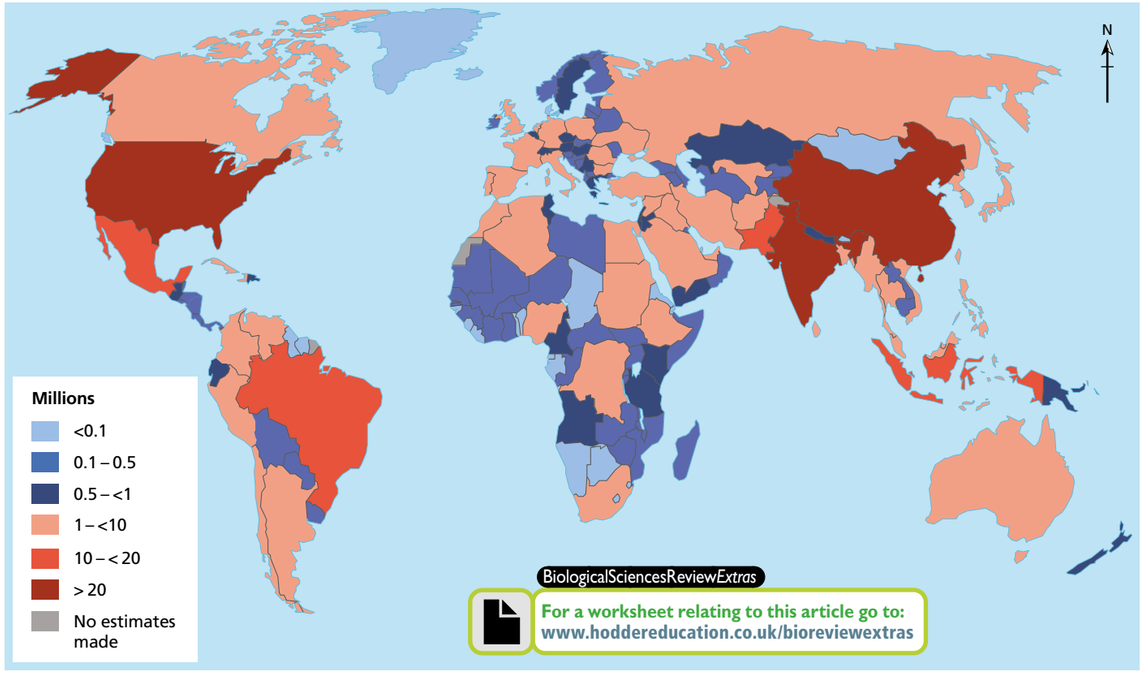


Figure 3 The number of people in each country who suffer with diabetes

products to their populations. It is therefore no surprise that both these countries have a high (and increasing) prevalence of type 2 diabetes.

In contrast, sub-Saharan Africa, which has a relatively lower rate of economic development, has a much lower prevalence of diabetes (see Figure 3). However, lower levels of development bring their own problems. Despite a lower overall prevalence, sub-Saharan Africa has a higher percentage of undiagnosed cases than any other continent. High levels of malnutrition and lack of healthcare also contribute to the risk of developing type 2 diabetes. As a result, despite a lower prevalence, sub-Saharan Africa has a higher diabetes-related mortality rate than any other continent, and twice that of Europe.

Education and healthcare

The CDC in the USA has reported that diabetes prevalence varies depending on level of education. In 2017–18, adults educated to less than a high-school level were almost twice as likely to develop diabetes than those educated to college/university level. This is in part due to income, as higher education in the USA is expensive. Additionally, globalisation means unhealthy fast food is generally more affordable than healthy nutritious food, hence why income can provide a link between diabetes and education. However, a lack of education is also likely to correspond to a poor understanding of how to maintain a healthy lifestyle, whether that be through diet or exercise.

Access to healthcare is a privilege in many countries, and treatment is not always available. Even in a developed country such as the USA, insulin can cost $200 a month, making it difficult for people without health insurance to obtain it. Globally, diabetes prevalence is expected to rise from the current 9% to 11% by 2045, affecting around 700 million people. In order to tackle this growing disease, we must focus on implementing global policies and strategies that focus on prevention and reduction of avoidable deaths. Educating younger generations of the risk factors, improving access to healthcare and medicine, and funding research into preventative measures and cures are all steps that will help to maintain a healthy global population and ease the burden of diabetes.

RESOURCES

Diabetes.co.uk has information on the causes and complications of diabetes, as well as an online community for those in need.

A clear overview of the different types of diabetes, their causes and their symptoms, produced by the charity Diabetes UK:
https://youtube.com/watch?v=X9ivR4y03DE

Topics for discussion

- How might living with diabetes affect your lifestyle?
- Why do you think educating young people about diabetes is so important?

Katy Walsh is a recent graduate in genetics from the University of Glasgow. She spent her work placement year at the University of Leeds investigating the impact of changes in maternal glucose concentrations on fetal growth and development in pregnancies affected by diabetes. She is currently studying for a PhD at The University of Manchester on a British Heart Foundation funded project on the cardiovascular complications of diabetes.