Global aetiology and epidemiology of type 2 diabetes mellitus and its complications

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Abstract | Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM). Asia is a major area of the rapidly emerging T2DM global epidemic, with China and India the top two epicentres. Although genetic predisposition partly determines individual susceptibility to T2DM, an unhealthy diet and a sedentary lifestyle are important drivers of the current global epidemic; early developmental factors (such as intrauterine exposures) also have a role in susceptibility to T2DM later in life. Many cases of T2DM could be prevented with lifestyle changes, including maintaining a healthy body weight, consuming a healthy diet, staying physically active, not smoking and drinking alcohol in moderation. Most patients with T2DM have at least one complication, and cardiovascular complications are the leading cause of morbidity and mortality in these patients. This Review provides an updated view of the global epidemiology of T2DM, as well as dietary, lifestyle and other risk factors for T2DM and its complications.

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The epidemic of diabetes mellitus and its complications poses a major global health threat. The International Diabetes Federation (IDF) estimated that 1 in 11 adults aged 20–79 years (415 million adults) had diabetes mellitus globally in 2015 (REF. 1). This estimate is projected to rise to 642 million by 2040, and the largest increases will come from the regions experiencing economic transitions from low-income to middle-income levels[1]. However, these estimates might have under-represented the true global burden of diabetes mellitus, especially in regions undergoing rapid epidemiological transitions[2]. The reasons for the escalating epidemic of diabetes mellitus are multiple, including population ageing, economic development, urbanization, unhealthy eating habits and sedentary lifestyles. Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM)[3,4]. However, types of diabetes mellitus are often not distinguished in population-level estimates; therefore, in this Review, the term diabetes mellitus refers to all types of diabetes mellitus unless otherwise specified. Although the genetic architecture might partially determine an individual's response to environmental changes[5], the main drivers of the global epidemic of T2DM are the rise in obesity, a sedentary lifestyle, energy-dense diets and population ageing[6]. Strong evidence indicates that many cases of T2DM could be prevented by maintaining a healthy body weight, following a healthy diet, exercising daily for at least 30 min, avoiding smoking and consuming alcohol in moderation[7,8].

In this Review, we describe the global trends of T2DM and its complications. We then discuss the roles of major risk factors, in particular, obesity, lifestyle factors, genetic predispositions, epigenetics and early developmental factors in the epidemic of T2DM and its complications. We highlight evidence from landmark large-scale intervention trials and longitudinal cohort studies from several countries and summarize recommendations for preventing T2DM and its complications.

Global burden of T2DM

T2DM and its complications have contributed tremendously to the burden of mortality and disability worldwide. For instance, the Global Burden of Disease Study 2013 identified diabetes mellitus (all forms) as the ninth major cause of reduced life expectancy[9]. In 2010, it was estimated that diabetes mellitus caused 3.96 million deaths in adults aged 20–79 years during that year (6.8% of global mortality)[10]. This estimate was raised to 5.0 million deaths due to diabetes mellitus and its complications during 2015 in an IDF report, which is equivalent to one death every six seconds[1]. The incidence of disability caused by diabetes mellitus has increased substantially

Key points

- Globally, about 1 in 11 adults have diabetes mellitus (90% have type 2 diabetes mellitus (T2DM)), and Asia is the epicentre of this global T2DM epidemic.
- The major driving factors of the global T2DM epidemic include overweight and obesity, sedentary lifestyle and increased consumption of unhealthy diets containing high levels of red meat and processed meat, refined grains and sugar-sweetened beverages.
- Given its global influence, it is essential to break the vicious cycle of diabetes mellitus begetting diabetes mellitus over generations by implementing effective strategies to prevent gestational diabetes mellitus.
- Among patients with T2DM, cardiovascular complications are the leading cause of morbidity and mortality, and kidney complications are highly prevalent in patients in Asia with diabetes mellitus.
- Major clinical trials have demonstrated that diet and lifestyle modifications are effective in preventing T2DM in high-risk individuals.
- T2DM management strategies including lifestyle modifications, social support and ensuring medication adherence are key to reducing the incidence of diabetes mellitus complications.

since 1990, with particularly large increases among people aged 15–69 years[11]. The Global Burden of Diseases, Injuries, and Risk Factors Study 2015 estimated that a high fasting level of glucose was the tenth most common global risk factor for disability-adjusted life years (DALYs) in 1990, fourth most common in 2005 and third most common in 2015, accounting for 143 million DALYs in 2015 and a 22% increase in DALYs from 2005 to 2015 (REF. 12).

The onset of diabetes mellitus frequently occurs years before the actual diagnosis. Globally, 45.8% (or 174.8 million cases) of all diabetes mellitus cases in adults were estimated to be undiagnosed[13]; people with undiagnosed and untreated diabetes mellitus are at a greater risk of complications than those who are receiving treatment. Furthermore, medical expenditure for patients with diabetes mellitus is up to three times greater than for the general population without diabetes mellitus[14]. The IDF conservatively estimated that in 2015, US$673 billion (12% of global health expenditure) was spent on treating diabetes mellitus and its related complications[1].

Globally, the number of people living with diabetes mellitus quadrupled between 1980 and 2014 (REF. 15). Between 2010 and 2030, a 20% increase in the number of adults with diabetes mellitus in developed countries and a 69% increase in developing countries has been predicted[16]. Asia has emerged as the major area with a rapidly developing T2DM epidemic. China and India are the top two epicentres of the global epidemic of T2DM[1] (FIG. 1). In these countries, the T2DM epidemic is characterized by onset at a lower BMI and younger age than in Western populations[17].

In China, a large-scale population-based survey was used to estimate that in 2010, >113.9 million adults (11.6% of the adult population) had diabetes mellitus and 493.4 million adults (50.1% of the total population) had prediabetes mellitus (impaired glucose tolerance, defined as 2-h oral glucose tolerance levels 7.8–11.0 $mmol^{-1}$, and impaired fasting glucose, defined as fasting glucose levels 6.1–6.9 $mmol^{-1}$, according to the WHO criteria)[18]. Less than one-third of those with diabetes mellitus had been previously diagnosed; only one-quarter of patients with diabetes mellitus had been treated, and only 39.7% among those treated had blood levels of HbA_{1c} < 7.0%[18]. In India, a national study estimated that 62 million individuals had diabetes mellitus and 77 million had prediabetes mellitus in 2011 (REF. 19). The IDF estimates that India will have 69.2 million patients with diabetes mellitus in 2015, with a projected rise to 123.5 million by 2040 (REF. 1). Based on data from India, China, Thailand and Malaysia, the cost of inpatients with diabetes mellitus but no complications accounted for 11–75% of per-capita income in 2007, with inpatients who had complications spending up to three times as much as those without complications[20].

The USA was listed as the country or territory with the third-highest number of patients with diabetes mellitus in 2015 (REF. 1) (FIG. 1), and half of adults aged 65 years or older had prediabetes mellitus in 2008 (REF. 21). Furthermore, the North America and Caribbean region, where the expenditure for diabetes mellitus per person is 85-fold that in southeast Asia, spent more on diabetes mellitus treatment than all other regions combined[1]. The Pacific nations have a particularly high prevalence of diabetes mellitus; >30% in American Samoa and 25% in some other islands in Polynesia and Micronesia[15]. The Middle East is another hot spot of the global diabetes mellitus epidemic, with the prevalence of diabetes mellitus among adults ranging from 9.5% in Oman[22] to 25.4% in Saudi Arabia[23]. Despite a paucity of updated regional data in Africa, IDF 2015 estimated a regional prevalence of 2.1–6.7% in sub-Saharan Africa[1]. According to the Global Burden of Disease report, diabetes mellitus was ranked as one of the leading causes of years of life lost and has a major impact in Latin American countries[24]. On average, 25% of health expenditure in Latin American countries is spent on treating diabetes mellitus and related complications, and the greatest economic burdens were seen in Mexico and Brazil[25]. Notably, given the variations in diagnostic methods and criteria used in individual reports to identify T2DM, along with the lack of national data in developing nations, all the current estimates are likely to be imprecise and are probably an underestimate of current disease burden[26].

The available global estimates and predictions of T2DM highlight the seriousness of the diabetes mellitus pandemic; however, these estimates have limitations. In the IDF report, direct nationwide data were lacking in half of the countries, and their estimates were extrapolated from other similar countries[1]. The accuracy and reliability of such extrapolations might be questionable. In addition, the number of patients with diabetes mellitus globally by 2015 (415 million) has already far surpassed what had been predicted in 2000 for 2030 by both the IDF (324 million) and the WHO (366 million)[2]. Therefore, it is important to use these statistics cautiously and critically, as they are probably underestimates.

With the rising prevalence of childhood obesity in many countries, the prevalence of T2DM is increasing in paediatric populations[27]. Children with T2DM tend to develop complications in early adulthood[27], which

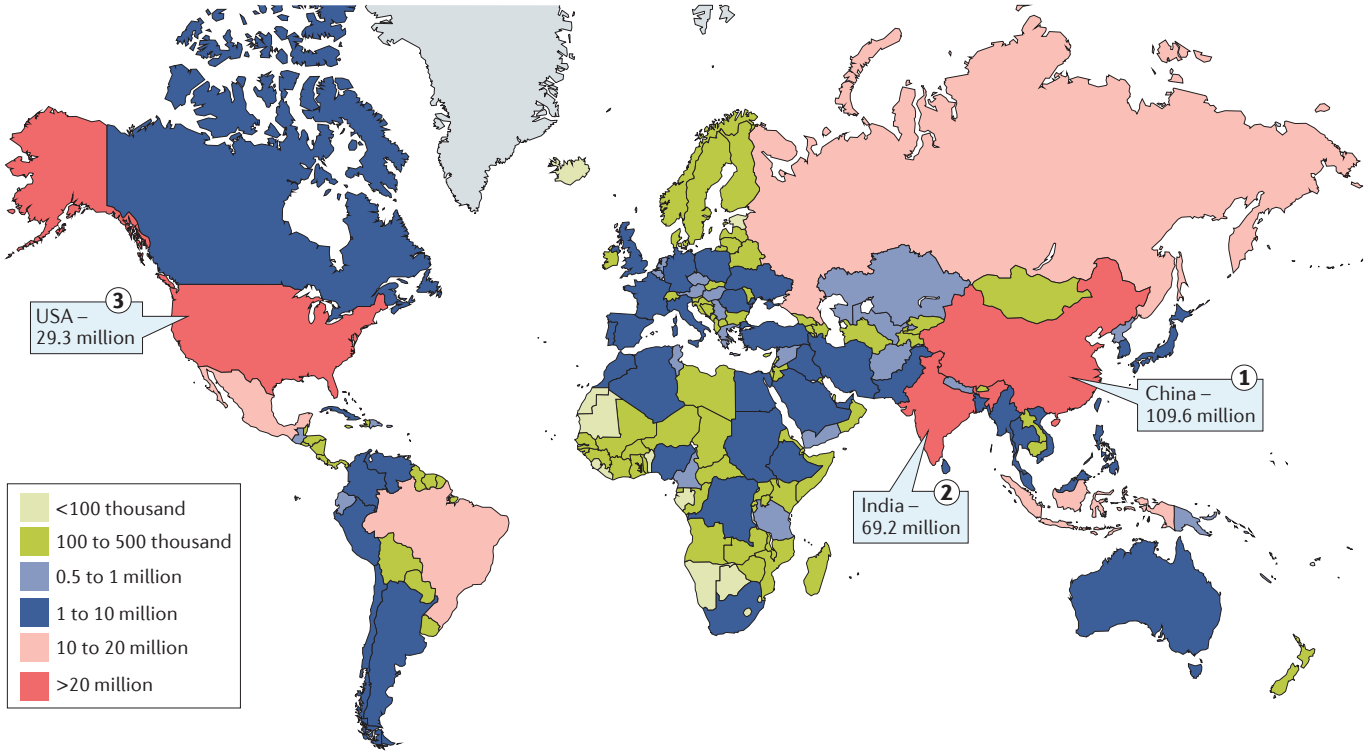

Figure 1 | **Estimated total number of adults (20–79 years) living with diabetes mellitus, highlighting the top three countries or territories for number of adults with diabetes mellitus (20–79 years) in 2015.** It was estimated that in 2015, 415 million adults aged 20–79 years had diabetes mellitus worldwide, and about 46.5% of them lived in three countries: China, India and the USA. The colour of the country or territory in the map relates to the total number of adults aged 20–79 years living with diabetes mellitus in the area. Figure adapted with permission from REF. 1, International Diabetes Federation Diabetes Atlas. IDF Diabetes Atlas, 7th edn Brussels, Belgium: International Diabetes Federation, 2015 http://www.diabetesatlas.org.

places a substantial burden on the family and society. Given its increasing prevalence, T2DM in childhood has the potential to become a global public health issue. Globally, the incidence and prevalence of T2DM in children and adolescents, with data that is predominantly only available from developed countries, were found to vary widely depending on ethnicity and geographical region[28]. In the USA, the prevalence of T2DM in children and adolescents has increased by 30.5% between 2001 and 2009 (REF. 29), and its incidence has increased 4.8% annually between 2002 and 2012 (REF. 30). T2DM disproportionately affects youth of ethnic minorities in the USA, such as Indigenous American people, African-American people and Hispanic people[28]. T2DM remains fairly uncommon in children under 10 years old, and most youth-onset cases were found in adolescents (10–19 years)[31]. Even so, data from China suggest that the prevalence of childhood T2DM has increased dramatically in the past two decades[32]. In India, preliminary data from a national registry of youth-onset diabetes revealed that 25% of patients with diabetes mellitus who were <25 years old had T2DM[33]. In countries such as the USA, Canada and Australia, the disproportionately higher incidence of T2DM with a trend of earlier age at onset was evident among indigenous populations compared with non-indigenous populations[34–36].

Pathophysiology and major risk factors

When the feedback loops between insulin action and insulin secretion do not function properly, the action of insulin in insulin-sensitive tissues such as liver, muscle and adipose tissue (insulin resistance in T2DM) and insulin secretion by pancreatic islet β-cells (β-cell dysfunction in T2DM) are affected, which results in abnormal blood levels of glucose[37] (FIG. 2). In T2DM, insulin resistance contributes to increased glucose production in the liver and decreased glucose uptake in muscle and adipose tissue at a set insulin level. In addition, β-cell dysfunction results in reduced insulin release, which is insufficient for maintaining normal glucose levels[38]. Both insulin resistance and β-cell dysfunction occur early in the pathogenesis of T2DM, and their critical importance has been verified longitudinally in Pima Indian people progressing from normal glucose tolerance to impaired glucose tolerance to T2DM[39].

In the past three decades, advances in epidemiological research on T2DM have improved our understanding of a wide range of risk factors for the development of T2DM. The determinants of T2DM consist of a matrix of genetic, epigenetic and lifestyle factors (BOX 1) that interact with one another and operate within the larger physical–sociocultural environment. Although individual predisposition to T2DM has a strong genetic basis, evidence from epidemiological studies suggests that many cases of T2DM can be prevented with lifestyle modifications[7,8].

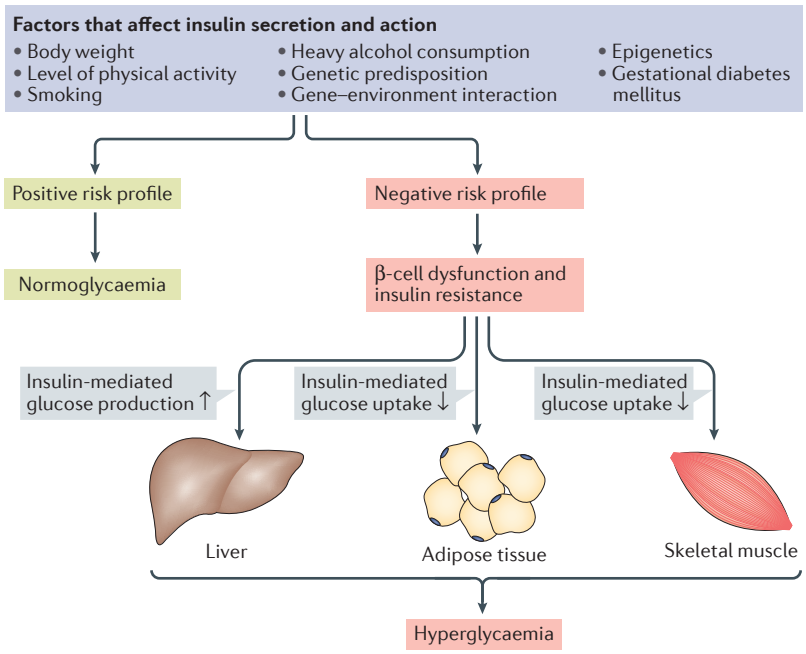

Figure 2 | **Pathophysiology of hyperglycaemia in T2DM.** Insulin secretion from the β-cells in the pancreas normally reduces glucose output by the liver and increases glucose uptake by skeletal muscle and adipose tissue. Once β-cell dysfunction in the pancreas and/or insulin resistance in the liver, skeletal muscle or adipose tissue occur, hyperglycaemia develops, leading to an excessive amount of glucose circulating in the blood. The various factors listed at the top affect insulin secretion and insulin action. T2DM, type 2 diabetes mellitus.

Overweight and obesity

The prevalence of T2DM is increasing in parallel with the escalating incidence of obesity in most developed countries, such as the USA[40], as well as in developing countries, such as China[18,41,42]. By contrast, a substantial reduction in the incidence of diabetes mellitus was observed following a population-wide reduction in body weight in the early 1990s in Cuba as a result of an economic crisis[43]. Globally, the age-standardized prevalence of obesity (defined as a BMI ≥30 kg/m^2) increased from 3.2% in 1975 to 10.8% in 2014 in men and from 6.4% to 14.9% in women[44]. If these trends continue, the global obesity prevalence is estimated to reach 18% in men and surpass 21% in women by 2025 (REF. 44). Excess adiposity, assessed by a high BMI, is the single strongest risk factor for T2DM[8,45] and is associated with many metabolic abnormalities that result in insulin resistance[46]. In the Nurses' Health Study, 61% of the T2DM cases could be attributed to overweight (defined as a BMI ≥25 kg/m^2)[8]. Furthermore, abdominal obesity assessed by waist circumference or waist-hip ratio predicts T2DM risk independent of BMI[47]. Weight gain since young adulthood, which occurs frequently and gradually during the middle life stage, is another independent predictor of T2DM[48]. In addition, visceral adiposity might be an independent predictor for T2DM risk[49].

In the USA, people of Asian descent are 30–50% more likely to develop diabetes mellitus at a much lower BMI than white people[50]. Such ethnic variations could be attributed to different fat distributions and percentages of body fat. For instance, Asian individuals generally have a higher total body fat percentage at a given BMI[51] and higher visceral adiposity than white people[17]. In addition, abdominal (or central) adiposity, high levels of which increase the risk of T2DM, is highly prevalent in Asian people[52]. Such ethnic heterogeneity in pathophysiology in T2DM could be attributable to the variations in both genetic background and phenotype; for example, Asian people without diabetes mellitus generally have poorer β-cell function than white people without diabetes mellitus[53].

At an individual level, treatment of obesity with weight loss surgery (for example, bariatric surgery) has proven effective in the prevention and resolution of T2DM[54]. However, this approach is expensive and is unlikely to reverse the current diabetes mellitus epidemic. Thus, population-level strategies for obesity prevention are critical. To address the dual epidemics of obesity and diabetes mellitus, we need to consider the root causes of these diseases, particularly unhealthy diet and lifestyle choices.

Diet and lifestyle factors

Diet and lifestyle modification is an important aspect of T2DM prevention. Major clinical trials have demonstrated that intensive lifestyle interventions can lower the incidence of diabetes mellitus by 58% compared with control groups[55]. Trials have also shown that these interventions are more effective than pharmacological interventions[55]. Landmark clinical trials, such as the Diabetes Prevention Program in multi-ethnic Americans[55], the Finnish Diabetes Prevention Study[56] and the Da Qing IGT and Diabetes Study in China[57], have demonstrated that many cases of T2DM could be prevented through lifestyle interventions focused on increasing physical activity and adopting a healthy diet. Nevertheless, when lifestyle interventions are not feasible, pharmacological therapy can be considered as a strategy to prevent the development of T2DM. For example, metformin reduced the incidence of T2DM by 31% over an average follow-up period of 2.8 years among high-risk individuals from the USA who did not have diabetes mellitus[55]. Similarly, metformin reduced T2DM risk in clinical trials in India and China[58].

As trial participants are generally high-risk, they do not represent the general population; therefore, it is difficult to generalize the results from trials to the general population. Evaluating the long-term effects of interventions is also difficult owing to high costs of long-term trials and lack of participant adherence to the intervention. From a public health perspective, the findings from clinical trials in high-risk populations should be considered together with evidence from large-scale observational studies with longer follow-up periods.

Diet. The main evidence from observational and interventional studies on the associations between the risk of T2DM and the intake of nutrients and food groups, as well as dietary patterns, is summarized in TABLE 1. A diet containing high-quality fats and carbohydrates (that is, low in *trans* fatty acids, high in polyunsaturated fatty acids[59] and with a low glycaemic index and glycaemic

load[60]) rather than low quality fats and carbohydrates is more important than the relative quantity of these nutrients for T2DM prevention[61]. Dietary recommendations for preventing T2DM typically promote diets rich in whole grains, fruits, vegetables, nuts and legumes and low in refined grains, red or processed meat and sugar-sweetened beverages[59]. Adherence to a high-quality diet, such as the Mediterranean diet[62], was strongly associated with a reduced risk of T2DM. In Asian countries, such as China and South Korea, a rapid nutritional transition in the past two to three decades that was characterized by increased energy intake from sugars, animal products and refined grains and reduced consumption of cereals is a major contributor to the T2DM epidemic[59]. Furthermore, undernutrition (for example, exposure to famine) during early life might increase the risk of T2DM later in life[63], which is discussed in detail in a subsequent section.

Physical activity. Increased physical activity is an essential component of all effective lifestyle-based trials for the prevention of T2DM. Prospective evidence has shown that both aerobic exercise and resistance training independently have beneficial effects on preventing T2DM[64]. One study has shown that spending more time on moderate-intensity and vigorous-intensity physical activity is beneficial for preventing insulin resistance, independent of time spent sedentary[65]. By contrast, another study found that time spent sedentary was associated with an increased risk of T2DM, regardless of physical activity[66].

Smoking. A meta-analysis found a dose–response relationship between the number of cigarettes smoked and risk of T2DM, and current smokers had a 45% higher risk of T2DM than non-smokers[67]. Moreover, a high level of exposure to second-hand smoke has been associated with an increased risk of T2DM[68]. Smokers are more likely to have central fat accumulation than non-smokers, and smoking is known to induce insulin resistance and compensatory insulin-secretion responses[69], which could explain the increased risk of T2DM in people who smoke. Education campaigns to reduce smoking should be a major public health strategy to curb the epidemic of T2DM, especially in China and India, which are epicentres of both T2DM and smoking[70].

Alcohol intake. Moderate consumption of alcohol has been associated with a reduced risk of T2DM[71]. A meta-analysis of 20 cohort studies found a U-shaped relationship between alcohol consumption and T2DM risk for both sexes, and the lowest risk of diabetes mellitus was observed among people who consumed 1-2 drinks per day[71]. There might be sex differences in the alcohol–T2DM relationship due to potential sex differences in alcohol pharmacokinetics (that is, alcohol processing and elimination), which depend largely on body composition[72]. In a randomized clinical trial involving postmenopausal women, moderate alcohol consumption (about 25 g per day) for 6 weeks improved insulin sensitivity[73]. However, the public health messages around moderate drinking need to be communicated cautiously within a culturally appropriate context, particularly considering the steady increase in alcohol consumption in many Asian countries[74] and the health burden of excess alcohol consumption in eastern Europe[75].

Genomics and gene–environment interactions

Even though many cases of T2DM could be prevented by maintaining a healthy body weight and adhering to a healthy lifestyle, some individuals with prediabetes mellitus are more susceptible to T2DM than others, which suggests that individual differences in response to lifestyle interventions exist[76]. Substantial evidence from twin and family studies has suggested a genetic basis of T2DM[77]. Over the past decade, successive waves of T2DM genome-wide association studies have identified >100 robust association signals, demonstrating the complex polygenic nature of T2DM[5]. Most of these loci affect T2DM risk through primary effects on insulin secretion, and a minority act through reducing insulin action[78]. Individually, the common variants (minor allele frequency >5%) identified in these studies have only a modest effect on T2DM risk and collectively explain only a small portion (~20%) of observed T2DM heritability[5]. It has been hypothesized that lower-frequency variants could explain much of the remaining heritability[79]. However, results of a large-scale sequencing study from the GoT2D and T2D-GENES consortia, published in 2016, do not support such a hypothesis[5].

Genetic variants might help reveal possible aetiological mechanisms underlying T2DM development; however, the variants identified thus far have not enabled clinical prediction beyond that achieved with common clinical measurements, including age, BMI, fasting levels of glucose and dyslipidaemia. A study published in 2014 linked susceptibility variants to quantitative glycaemic traits and grouped these variants on the basis of their potential intermediate mechanisms in T2DM pathophysiology: four variants fitted a clear insulin resistance pattern; two reduced insulin secretion with fasting hyperglycaemia; nine

Box 1 | **Major risk factors for T2DM**

- Older age
- Non-white ancestry
- Family history of type 2 diabetes mellitus (T2DM)
- Low socio-economic status
- Genetic factors (for example, carrying risk alleles in the *TCF7L2* gene)
- Components of the metabolic syndrome (increased waist circumference, increased blood pressure, increased plasma levels of triglycerides, low plasma levels of HDL cholesterol and small, dense LDL cholesterol particles)
- Overweight or obese (BMI ≥25 kg/m^2)
- Abdominal or central obesity (independent of BMI)
- Unhealthy dietary factors (regular consumption of sugary beverages and red meats and low consumption of whole grains and other fibre-rich foods)
- Cigarette smoking
- Sedentary lifestyle
- History of gestational diabetes mellitus or delivery of neonates >4 kg in weight
- Some medications, such as statins, thiazides and beta-blockers
- Psychosocial stress and depression

Table 1 | **Associations between nutritional factors the risk of T2DM**

Nutritional factor assessed	Relative risk (95% CI)	Refs
Nutrients		
Haeme (iron)	1.31 (1.21–1.43) extreme groups*	143
Glycaemic index	1.19 (1.14–1.24) extreme groups*	60
Glycaemic load	1.13 (1.08–1.17) extreme groups*	60
Docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA)	1.04 (0.97–1.10) per 250 mg per day	144
Vegetable fibre	1.04 (0.94–1.15) extreme groups*	145
Fruit fibre	0.96 (0.88–1.04) extreme groups*	145
α-Linolenic acid	0.93 (0.83–1.04) per 0.5 g per day	144
Magnesium	0.78 (0.73–0.84) extreme groups*	146
Cereal fibre	0.67 (0.62–0.72) extreme groups*	145
Vitamin D	0.62 (0.54–0.70) extreme groups*	147
Food groups		
Processed red meat	1.51 (1.25–1.83) per 50 g per day	148
Unprocessed red meat	1.19 (1.04–1.37) per 100 g per day	148
Fish or seafood	1.12 (0.94–1.34) per 100 g per day	144
White rice	1.11 (1.08–1.14) per 1 serving per day	149
Green leafy vegetables	0.86 (0.77–0.97) extreme groups*	150
Green leafy vegetables	0.84 (0.74–0.94) extreme groups*	151
Dairy products	0.86 (0.79–0.92) extreme groups*	152
Whole grains	0.68 (0.58–0.81) per 3 servings per day	153
Sugar-sweetened beverages	1.26 (1.12–1.41) extreme groups*	154
Sugar-sweetened beverages	1.18 (1.06–1.32) per 336 g per day	155
Decaffeinated coffee	0.80 (0.70–0.91) extreme groups*	156
Total coffee	0.70 (0.65–0.75) extreme groups*	156
Dietary patterns		
Mediterranean diet	0.60 (0.43–0.85) Mediterranean diet supplemented with extra-virgin olive oil compared with control group (advice on a low-fat diet), 0.82 (0.61–1.10) Mediterranean diet supplemented with nuts compared with control group	62
Alternate healthy eating index (AHEI) 2010	0.77 (0.67–0.88) the highest compared with the lowest quintiles	157
Dietary approaches to stop hypertension (DASH)	0.75 (0.65–0.85) the highest compared with the lowest quintiles	157

T2DM, type 2 diabetes mellitus. *For the different categories of nutrients and food groups, such as the tertiles, quartiles or quintiles, the effect estimates and corresponding 95% CIs of extreme groups were calculated by comparing the highest and lowest categories in a meta-analysis.

reduced insulin secretion with normal fasting glycaemia; and one altered insulin processing[80]. Considering such evidence, the genetic architecture of T2DM is highly polygenic, and thus, substantially larger association studies are needed to identify most T2DM loci, which typically have small to modest effect sizes[81].

The missing heritability of T2DM could be accounted for by the interactions between susceptibility loci and various environmental determinants, whereby the impact of a given genetic variant is modified by the environmental milieu (and vice versa). Evidence that lifestyle factors modify the genetic effects on T2DM risk has been generated from both observational studies and clinical trials[82]. However, genetic background might also affect the individual's response to lifestyle interventions[83]. In addition, replication data are sparse, and comprehensive, large-scale studies have failed to provide a compelling basis for the significant interaction effect[84,85]. This failure might have occurred because the interaction effects are of small magnitude or might be due to the limited statistical power and multiple sources of bias and confounding factors in the current research methods[86].

Biomarkers and metabolomics

Over the past two decades, biomarkers from the pathways of abnormal adipocyte signalling, subclinical inflammation, endothelial dysfunction and iron overload have improved our understanding of the complexity of T2DM pathophysiology, beyond the classic triumvirate of β-cell, skeletal muscle and liver[87]. However, the ability of these biomarkers to predict future risk of T2DM beyond anthropometric measures, lifestyle factors and fasting levels of glucose and lipids is still debatable[87].

Within the past 7 years, a complementary, novel set of T2DM biomarkers has largely been generated by metabolomic studies, which systematically analyse metabolites (low molecular weight biochemicals) in a biological sample. A meta-analysis of published metabolomics studies that was published in 2016 revealed that the high circulating levels of hexoses, branched-chain amino acids, aromatic amino acids, phospholipids and triglycerides, were associated with the incidence of prediabetes mellitus and T2DM[88]. As downstream end products, levels of these metabolites could reflect upstream gene function and environmental influences, as well as their complex interplays. Of note, the metabolomics-derived indices enable statistically significant improvement in the prediction of T2DM risk beyond the use of traditional risk factors[89].

Developmental origins of T2DM

The thrifty genotype hypothesis postulates that thrifty genotypes favouring efficient metabolism and storage of energy were positively selected for as a result of evolutionary selection by repeated feast and famine cycles; these genotypes are maladaptive in many modern environments[90]. This hypothesis has been widely used to explain the disproportionate burden of T2DM among indigenous populations (worldwide, >50% of indigenous adults >35 years old are estimated to have T2DM)[91]. This selection might have led to increased vulnerability to diabetes mellitus among indigenous populations at a time of rapid transition to a high-calorie diet and physical inactivity[91].

In contrast to the thrifty genotype hypothesis, the thrifty phenotype hypothesis (developmental origins) postulates a mismatch between early developmental environments (intrauterine) and adulthood environments. This hypothesis proposes that the adaptations in response to fetal undernutrition that lead to metabolic and structural changes (for example, decreased β-cell mass and function and increased insulin resistance) are beneficial for early survival but might increase the risk of chronic diseases, such as T2DM, in adulthood[92]. Low birthweight, a widely

used indicator of fetal undernutrition, is associated with an increased risk of T2DM in adult life[93]. Epidemiological evidence from the Dutch Hunger Winter of 1944–1945 (REF. 94) and the Chinese famine of 1958–1962 (REF. 63) shows that children born during a famine who are exposed to intrauterine undernutrition but live in an obesogenic environment as an adult have an increased risk of chronic diseases (including T2DM). Epigenetic processes could be a central underlying mechanism of this thrifty phenotype hypothesis, leading to altered feeding behaviour, insulin secretion and action and even transgenerational risk transmission[95].

Gestational diabetes mellitus, which is a common pregnancy complication defined as glucose intolerance with onset or first recognition during pregnancy[96], is another risk factor that influences T2DM risk in exposed women and their offspring. The prevalence of gestational diabetes mellitus varies depending on the diagnostic criteria used and the study population; for instance, the prevalence is 1.2–3.1% of pregnancies in European countries (except for Italy) and 1.9–13.7% of pregnancies in the southeast Asia region[97]. Women with gestational diabetes mellitus had a sevenfold increased risk of developing T2DM compared with those who had a normoglycaemic pregnancy[98]. In the offspring of women with gestational diabetes mellitus, exposure to intrauterine hyperglycaemia is a strong risk factor for T2DM[96]. The increasing frequency of exposure to gestational diabetes mellitus *in utero*, together with increasing body weight, accounted for most of the increase in the prevalence of T2DM in Pima Indian children[99]. Given its global influence, it is essential to break the vicious cycle of diabetes mellitus begetting diabetes mellitus over generations by implementing effective strategies to prevent gestational diabetes mellitus.

Other factors

Interest in the role of the gut microbiome in the development of T2DM has exploded in the past few years, and variation in the diversity and composition of the gut microbiota has been tied to T2DM[100]. For example, levels of butyrate-producing bacteria are decreased in the gut microbiota of patients with T2DM compared with that of healthy individuals[101]. In addition, evidence suggests that ambient air pollution is an emerging risk factor for T2DM[102], especially in developing countries where the rapid increase in urbanization has introduced high levels of outdoor and indoor pollution[103,104]. Furthermore, the use of some medications, such as statins, thiazides and beta-blockers, has been associated with an increased risk of T2DM[105].

Epidemiology of complications in T2DM

The complications of diabetes mellitus have traditionally been divided into macrovascular complications (for example, cardiovascular disease (CVD)) and microvascular complications (for example, complications affecting the kidney, the retina and the nervous system). Complications of T2DM are very common, with half of patients with T2DM presenting with microvascular complications and 27% with macrovascular complications in an observational study of 28 countries in Asia, Africa, South America and Europe[106]. On the basis of cohort studies from developed countries, the relative risk of microvascular disorders and macrovascular disorders among patients with diabetes mellitus was estimated to be at least 10–20 times higher and 2–4 times higher, respectively, than in people without diabetes mellitus[107]. In most developing countries, patients with diabetes mellitus are at a particularly increased risk of developing kidney complications and stroke (but have a reduced risk of coronary heart disease) compared with patients in developed countries[108].

The large increase in the number of prevalent cases of diabetes mellitus and undiagnosed diabetes mellitus, together with advances in the treatment of T2DM meaning that people are living longer with the condition than they used to, has resulted in a costly increase in the incidence of diabetic complications; for instance, 53% of the lifetime medical costs of T2DM have been attributed to treating the major complications of T2DM (nephropathy, neuropathy, retinopathy, stroke and coronary heart diseases) in the USA[109]. However, the absence of internationally recognized and standardized classification, definition or diagnostic criteria for the complications of T2DM makes it hard to precisely estimate their contributions to morbidity and mortality[26]. Patient-centred management of T2DM involves lifestyle modification and combination therapy of medication[110]. In some developed countries, the management of T2DM, mainly through glycaemic control and cardiovascular risk management, has resulted in improved care; however, for the rest of the world, such data are scarce[107].

Cardiovascular disease

CVD, including coronary heart disease, peripheral vascular disease and cerebrovascular disease, is the primary cause of morbidity and mortality in the USA[21]. In patients with T2DM, CVD typically develops 14.6 years earlier[111], and with greater severity, than in individuals without diabetes mellitus[112]. Furthermore, individuals with T2DM are twice as likely to develop CVD as those without T2DM, independent of age, smoking status, BMI and systolic blood pressure[113], and diabetes mellitus has been associated with a more than doubled risk of death from vascular causes[114]. This excess risk disproportionately affects women[115] such that diabetes mellitus eliminates or attenuates the reduced risk of CVD that is generally seen in premenopausal women. Post hoc analysis of data from the large-scale, randomized clinical trial Action in Diabetes and Vascular Disease (ADVANCE) has suggested that patients from Asian countries who have T2DM have a lower risk of major coronary events than patients from eastern Europe or Established Market Economies[116]. Within Asia, susceptibility to vascular complications varies across ethnicities and areas. For example, patients in China with diabetes mellitus had lower rates of coronary artery disease than patients in other countries[117], whereas patients in India who had T2DM had a doubled risk of coronary artery disease-related deaths compared with white Europeans who had T2DM, independent of traditional risk factors[118]. Coronary artery disease detection and diabetes mellitus duration in these studies might partially account for the ethnic differences.

Renal disease

Approximately 10% of deaths in people with T2DM are attributable to renal failure[119]. Diabetes mellitus causes 44% of the incident cases of end-stage renal disease (ESRD) in the USA[21]. Furthermore, in the USA, about 25% of patients with T2DM have diabetic kidney disease, which is defined as persistent albuminuria, persistent reduced estimated glomerular filtration rate or both[120]. In China, glomerulonephritis was historically the leading cause of ESRD; however, diabetes-related chronic kidney disease was the leading cause of ESRD in the general population in 2010 and has been the leading cause in hospitalized patients since 2011 (REF. 121). In North America, diabetes-related ESRD is 80% more prevalent in patients with T2DM of Asian descent than in patients who are white[122]. Furthermore, the risk of diabetic kidney disease is much higher in Asian countries than in Western countries[17]. The ADVANCE trial has confirmed the increased frequency of renal disease in patients with diabetes mellitus in Asia compared with white patients in eastern Europe and Established Market Economies[116]. Genetic background, lifestyle and patient awareness of complications might account for these ethnic differences in renal disease among patients with diabetes mellitus[123].

Other complications

The prevalence of diabetic retinopathy is approximately 28.5% in the USA[124] and ranges from 16% to 35% in Asian countries[125,126]. T2DM is the leading cause of non-traumatic lower-limb amputations in the USA[21]. In the UK, about one in three amputees has diabetes mellitus[127], and in Australia, about half of amputees have diabetes mellitus[128]. Directly or indirectly, T2DM might also increase the risks of disorders in the musculoskeletal, hepatic and digestive systems, as well as cognitive function and mental health disorders, and could increase the incidence of some cancers, for instance, those of the liver, pancreas and endometrium[129]. Several key comorbidities, such as non-alcoholic fatty liver disease[130], obstructive sleep apnoea[131] and depression[132], are associated with T2DM bi-directionally, and such interrelationships are at least partially caused by obesity. However, the paucity of population-level data on the associations of T2DM with these diseases and other complications, such as infections and neuropathy, is a major gap in population-level monitoring.

T2DM management

Modification of lifestyle, including weight loss, increasing physical activity and adopting a healthy diet, remains one of the first-line strategies for the management of T2DM. In the Look AHEAD (Action for Health in Diabetes) trial in the USA[133], a 4-year intensive lifestyle intervention through caloric restriction and increased physical activity achieved increased weight loss, improved cardiometabolic risk profiles and a reduced requirement for medication to control CVD risk factors compared with the control group (who had diabetes mellitus and received support and education about lifestyle modifications)[134]. However, after a median follow-up period of 9.6 years, the trial was terminated because the intervention did not reduce the rate of CVD events[134].

Another randomized, controlled trial in the USA, the Health Benefits of Aerobic and Resistance Training in Individuals with Diabetes (HART-D) trial, found that HbA_{1c} levels were reduced in the group that undertook combined resistance and aerobic training after the 9-month exercise program, but not in the group that undertook either resistance training or aerobic training alone[135]. These findings suggest that it is more beneficial to combine both aerobic and resistance exercises than to perform only one type of exercise when time available to exercise is limited[136]. The post hoc subgroup analysis of data from the PREDIMED trial, which was conducted in Spain, revealed that a Mediterranean diet significantly reduced CVD risk (by ~30%) in participants with diabetes mellitus[137]. Furthermore, a Mediterranean diet enriched with extra-virgin olive oil might protect against diabetic retinopathy, but not against diabetic nephropathy[138].

In addition to lifestyle modification, social support has an important role in T2DM management as it directly affects the performance of diabetes mellitus self-care behaviours and indirectly affects glycaemic control[139]. For example, patients whose family members exhibit non-supportive behaviours have reduced adherence to diabetes mellitus medication regimens[140]. Public health and social interventions through a multifaceted systems approach, involving structural changes in schools, workplaces, communities, media and food and beverage systems, have been proposed to address the pandemic of obesity[141], and these are also applicable to T2DM prevention and management.

Conclusions

In the past three decades, T2DM and its complications have reached epidemic levels, particularly in developing countries. T2DM is a global crisis that threatens the health and economy of the world. Approximately 1 in every 11 adults has T2DM globally, and about 75% of patients with diabetes mellitus live in developing countries[1]. T2DM is associated with an 8-year reduction in lifespan in the USA[142], and also has a negative effect on quality of life as most patients also have complications. About 12% of the global health expenditure was spent on treatment of T2DM and its related complications in 2015 (REF. 1).

An accumulating body of evidence from large prospective observational studies and randomized clinical trials indicates that many cases of T2DM could be prevented by maintaining a healthy body weight with a focus on maintaining energy balance by engaging in regular physical activity and consuming a healthy diet[7,8]. Preventing and managing gestational diabetes mellitus to stop the vicious cycle in which diabetes mellitus begets diabetes mellitus is also key. The mismatch between early developmental environment (for example, fetal undernutrition) and obesogenic adulthood environment is an important risk factor for T2DM. For T2DM management, lifestyle modification, social support and medication adherence are important for reducing the risk of cardiovascular and other complications.

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