

Type 2 diabetes mellitus

Melanie J. Davies^{1,2}✉, Soo Lim³, Tommy Slater^{1,2}, Jonathan Goldney^{1,2}, Athena Philis-Tsimikas⁴, Denise R. Franco⁵, Roberta Lamptey⁶, Thomas Yates^{1,2}, Tsvetalina Tankova^{7,8} & Ildiko Lingvay⁹✉

Abstract

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease driven by a complex interplay of genetic, biological, behavioural and social factors. The epidemiology of T2DM has shifted considerably, largely attributable to increasing obesity rates. Furthermore, T2DM prevalence is increasing in younger people (diagnosis <40 years of age; early-onset T2DM), which is associated with more aggressive disease progression, higher risk factor burden, earlier and more severe complications, and greater lifetime morbidity than later-onset T2DM. T2DM is traditionally associated with a high risk of microvascular and macrovascular complications, although rates of cardiovascular complications have reduced in some high-income countries. Currently, emerging and non-traditional diabetes complications, such as those related to mental health and cognitive function, are being recognized, and people with T2DM increasingly experience multimorbidity and reduced quality of life. Additionally, a growing prevalence of obesity has resulted in high rates of obesity-related complications. Novel therapies and technologies may offer considerable benefit, although socioeconomic disparities may exacerbate barriers to effective prevention and equitable access. The complex nature of T2DM and its comorbidities underscores the urgent need for a person-centred, holistic approach that integrates glucose and weight management with broader attention to comorbidities, 24-h physical behaviours, psychosocial well-being and social determinants of health.

Sections

[Introduction](#)[Epidemiology](#)[Mechanisms/pathophysiology](#)[Diagnosis, screening and prevention](#)[Management](#)[Quality of life](#)[Outlook](#)

¹Diabetes Research Centre, College of Life Sciences, University of Leicester, Leicester General Hospital, Leicester, UK. ²NIHR Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust, Leicester, UK.

³Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea. ⁴Scripps Whittier Diabetes Institute, Scripps Health, San Diego, CA, USA.

⁵CPClin/DASA Clinical Research Centre, São Paulo, Brazil. ⁶Korle Bu Polyclinic Family Medicine Department, Korle Bu Teaching Hospital, Accra, Ghana. ⁷Department of Endocrinology, Faculty of Medicine, Medical University, Sofia, Sofia, Bulgaria. ⁸Department of Diabetology, University Hospital of Endocrinology, Sofia, Bulgaria. ⁹Department of Internal Medicine/Endocrinology and Peter O'Donnell Jr School of Public Health, University of Texas Southwestern Medical Center, Dallas, TX, USA. ✉e-mail: melanie.davies39@nhs.net; ildiko.lingvay@UTSouthwestern.edu

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease characterized by persistently elevated blood glucose concentrations, which manifests through a complex interplay between genetic, biological, behavioural, psychological and social factors. The epidemiology of T2DM has evolved considerably since the early 2000s. Historically, T2DM was considered a disease of later life; however, prevalence is now increasing rapidly in young individuals^{1,2}, referred to as early-onset T2DM (EOT2D; diagnosis age <40 years). EOT2D is characterized by a more adverse risk factor profile, higher rates of complications and a greater lifetime disease burden as it presents during a productive phase of life (that is, education, employment and family planning) than later-onset T2DM^{3–5}. Complications of diabetes mellitus, such as microvascular and macrovascular complications, in particular cardiovascular diseases, have traditionally dominated the focus of guideline-driven prevention and management strategies. However, other emerging and non-traditional diabetes complications, such as those related to mental health, cognitive function and quality of life, are receiving increasing attention in the field^{6,7}. Thus, although there have been reported reductions in rates of cardiovascular complications in some high-income countries⁸, the symptomatic burden is increasing as the number of individuals living with diabetes mellitus and multiple long-term conditions (defined as the presence of two or more conditions) is rising rapidly^{9,10}, negatively affecting quality of life^{11,12} and creating greater pressure on healthcare services^{10,11,13,14}.

The rapidly increasing prevalence of overweight and obesity has resulted in a high incidence of comorbid obesity-related complications in people with T2DM such as obstructive sleep apnoea, metabolic dysfunction-associated steatotic liver disease (MASLD) and certain obesity-associated cancers^{15,16}. Low-income and middle-income countries (LMICs)^{17,18} and areas of low socioeconomic status bear a disproportionately high burden of T2DM, where resource constraints may preclude effective population-based prevention and management strategies and access to novel medications and technologies¹⁹. The complex nature of T2DM and its comorbidities necessitates a multifaceted, person-centred approach to prevent complications and maintain a good quality of life. This transition away from a traditional glucose-centric approach towards a more holistic model has become a priority in diabetes mellitus care globally²⁰. The change in care approach is further aided by the rapidly evolving landscape of glucose-lowering and weight-lowering pharmacotherapies, which have demonstrated wide-ranging health benefits beyond hyperglycaemic control^{21,22}.

In this Primer, we review the epidemiology, pathophysiology, diagnosis and management (present and future) of T2DM. Furthermore, we highlight the effect of T2DM on the quality of life of patients and discuss avenues for future research.

Epidemiology

Incidence and prevalence

Since the 1950s, T2DM has exploded from a relatively uncommon condition to a global pandemic, driven primarily by lifestyle shifts towards sedentary living and poor diets, leading to widespread obesity, alongside genetic predispositions. T2DM has evolved from being a rare disease seen by physicians only a handful of times in their careers to affecting 1 in 7 adults currently in the USA, with higher prevalence in older individuals (1 in 4)^{23–25} and racial or ethnic minorities (1 in 3)²⁶, transforming it into a leading public health crisis comparable to infectious diseases. Globally, the number of adults with diabetes mellitus has more than tripled

between 1980 and 2021 (ref. 2). This increased trend is particularly pronounced in LMICs, where rapid urbanization and changing dietary and physical activity patterns have fuelled increasing rates of overweight and obesity, including in youth^{27,28}. In 2022, 828 million adults were estimated to have diabetes mellitus globally, which was 630 million more than in 1990. In addition, age-standardized prevalence reached 13.9% in women and 14.3% in men²⁹. Although T2DM predominantly occurred in older individuals, the incidence and prevalence of T2DM have substantially increased in youth (<18 years of age) and young adults (18–40 years of age; EOT2D)³⁰. In the USA, EOT2D disproportionately affects minoritized groups (Black, Hispanic and Indigenous) owing to complex factors, including social determinants of health such as poverty, structural racism and food or housing insecurity, which drive increased obesity and risk of T2DM, alongside potentially distinct genetic predispositions, with EOT2D often having a stronger genetic component than later-onset T2DM^{31,32}. These disparities highlight critical needs for community-specific interventions addressing upstream social factors and tailored genetic screening, especially as EOT2D carries elevated risks for complications and premature mortality.

The most substantial increases in T2DM prevalence occurred in LMICs within Southeast Asia (for example, Malaysia), South Asia (for example, Pakistan), the Middle East and North Africa (for example, Egypt) and Latin America and the Caribbean (for example, Jamaica, Trinidad and Tobago and Costa Rica) and in small-island developing states, including the Federated States of Micronesia and Vanuatu²⁹ (Fig. 1). The latest International Diabetes Federation statistics show that the overall prevalence of diabetes mellitus (~90% of which is T2DM) in sub-Saharan African countries is low, at 5%, but it is predicted to increase by 142% to 60 million people by 2050 (ref. 2). Despite the expanding burden, treatment coverage remains inadequate – in 2022, among an estimated 445 million adults ≥30 years of age with diabetes, ~59% were untreated, which is 3.5-fold higher than in 1990 (ref. 29). However, these numbers must be interpreted with caution. The inherent heterogeneity in diagnostic criteria, surveillance methods and data quality across different regions suggests that true comparisons of T2DM prevalence and incidence worldwide remain a major challenge. Greater standardization in data collection and diagnostic approaches is required globally to improve the accuracy of public health assessments and ensure that targeted interventions are effective.

To address these disparities, a multidisciplinary consensus initiative has proposed a framework to advance the prevention and care of T2DM across diverse populations^{33,34}. Although several high-income countries and emerging economies have achieved substantial advancements in treatment access and glycaemic control since the 2000s, such progress has been laborious in LMICs, exacerbating the global disparity in prevalence and care. As a result, an increasing share of the global diabetes burden, particularly among untreated individuals, now exists in LMICs.

Risk factors

The biological dysregulation that leads to hyperglycaemia occurs owing to a mixture of genetic and environmental influences. Environmental exposures, health-related behaviours and subsequent T2DM risk are determined by intersecting social determinants of health³⁵ (Fig. 2). These social determinants range from societal factors, including public policy, public health, culture and food security, to community-level factors, such as community walkability, the built environment, housing quality and air pollution³⁶, down to individual-level factors such as loneliness, social support, employment status, income, social class,

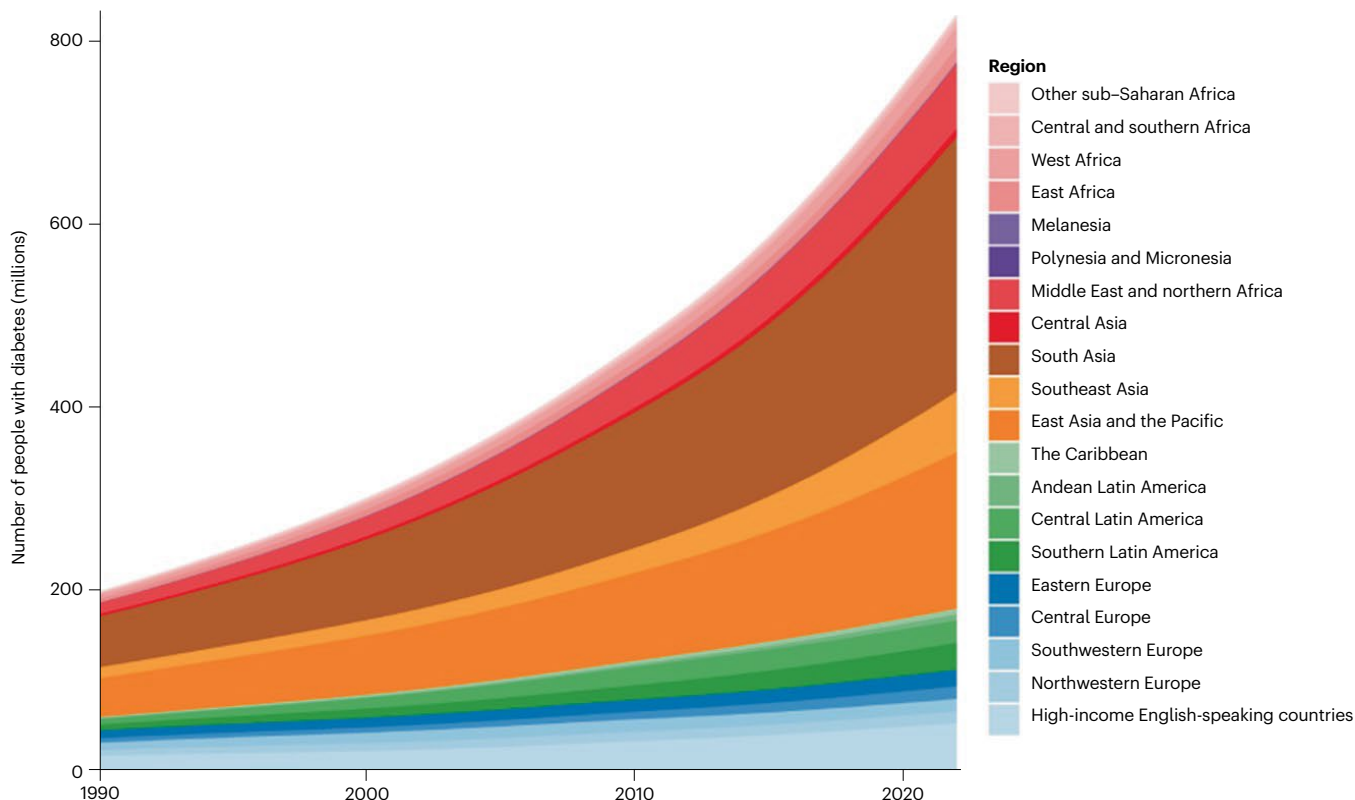


Fig. 1 | Changes in global prevalence of diabetes between 1990 and 2020. The estimated number of people living with diabetes (inclusive of type 1 diabetes mellitus and type 2 diabetes mellitus) between 1990 and 2022 by region. Adapted from ref. 29, CC BY 4.0.

and early childhood education and development, all of which intersect with the traditional risk factors for T2DM.

Traditional risk factors for developing T2DM are well described and encompass several behavioural, lifestyle and biological factors (Fig. 2). Excess adiposity, reflected in the continued increase in the prevalence of overweight and obesity², is the major factor contributing to the development of T2DM. Modifiable lifestyle factors, including unhealthy food choices (diet high in red and processed meats, refined carbohydrates and sugar-sweetened beverages, low in nuts, seeds and whole grains), alcohol consumption, physical inactivity, poor sleep hygiene, smoking, depression and stress, are all associated with T2DM³⁷. One analysis estimated that, in 2018, 14.1 million new T2DM cases were attributable to suboptimal intake of the analysed dietary factors, representing >70% of new diagnoses globally³⁸. The largest T2DM burdens were attributable to insufficient whole-grain intake (26.1% (95% CI 25.0–27.1%)), excess refined rice and wheat intake (24.6% (95% CI 22.3–27.2%)) and excess processed meat intake (20.3% (95% CI 18.3–23.5%)). Non-modifiable risk factors include older age (greatest risk observed in those aged >65 years), family history of T2DM, birthweight and ethnic background, with people of Asian, African and Afro-Caribbean ethnicity having a greater risk of developing T2DM than white individuals³⁹.

Mortality

T2DM and its associated complications contribute substantially to worldwide mortality. The WHO report on diabetes mellitus mortality showed that the mortality owing to diabetes increased by 3% from 2000

to 2019 (refs. 40–42). By contrast, the probability of dying from any one of the four main non-communicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes mellitus) between 30 and 70 years of age decreased by 20% globally between 2000 and 2019. In 2024, 3.4 million adults died as a result of diabetes mellitus or its complications, which corresponds to 9.3% of deaths from all causes². T2DM constitutes >90% of all diabetes mellitus cases globally², indicating that the vast majority of diabetes-related deaths are owing to T2DM. T2DM is associated with increased risk of mortality from several causes, including cardiovascular, renal and liver disease, certain cancers, and infections.

The effect of T2DM on mortality varies across age, geographical location and ethnicity. For example, socioeconomic deprivation is independently associated with mortality risk in people with T2DM⁴³. Age at the time of T2DM diagnosis might also impact mortality. Estimates suggest that people with diabetes mellitus die, on average, 6 years earlier than people without diabetes mellitus⁴⁴. One observational study calculated age-adjusted and sex-adjusted hazard ratios for all-cause mortality according to age at diagnosis of T2DM⁴⁵. Findings indicate that every decade of earlier diagnosis of diabetes mellitus was associated with 3–4 years of reduced life expectancy. Although people diagnosed later in life have an increased absolute risk of mortality, relative rates of all-cause, cardiorenal, and non-cancer and non-cardiorenal mortality have been shown to be greater in those with EOT2D than in those diagnosed later in life⁴.

In several parts of the world, temporal trends have illustrated declining mortality in people with T2DM^{46,47}. In the UK, all-cause

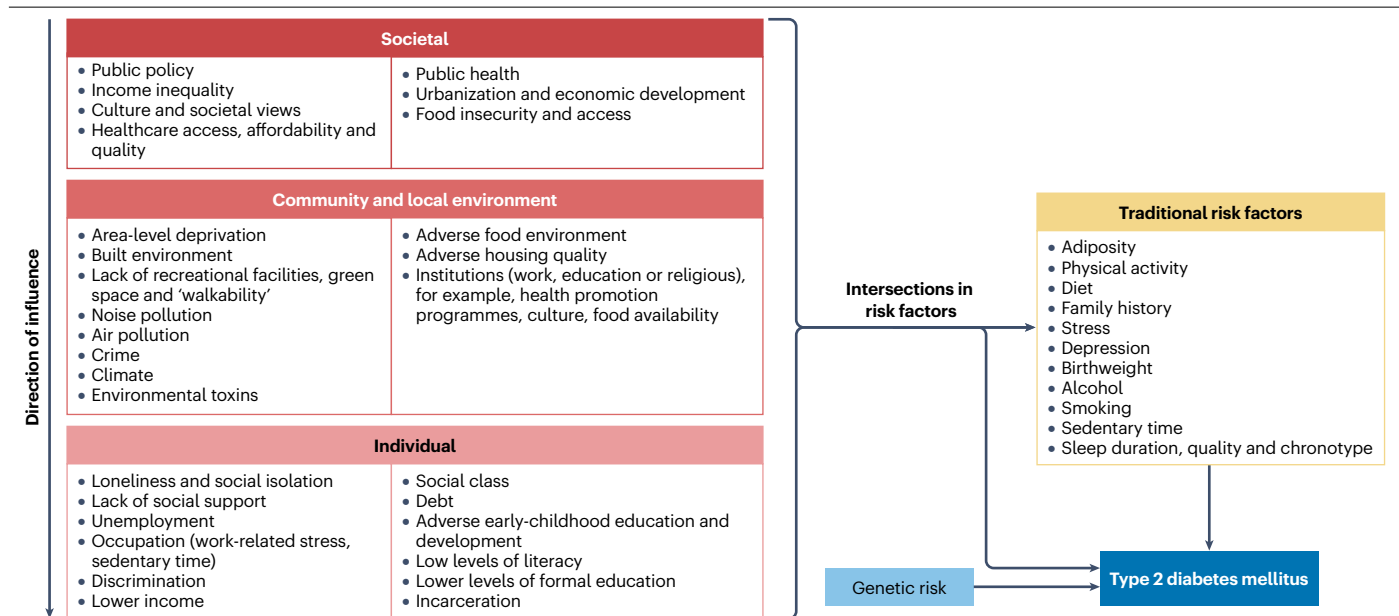


Fig. 2 | Social determinants of T2DM risk. Numerous social determinants have been established as risk factors of type 2 diabetes mellitus (T2DM), including societal-level factors, community-level and local environment-level factors,

and individual-level factors. These social determinants cause and intersect with 'traditional risk factors', which, alongside genetic risk, lead to the development of T2DM.

mortality declined in adults with T2DM between 2009–2011 and 2018–2019, primarily owing to reductions in cardiovascular-related fatalities⁴⁸. Interestingly, during the same time frame, no change was observed in all-cause mortality in white individuals but a decline in all-cause mortality was observed in those of South Asian ancestry. Furthermore, people living in the least socioeconomically deprived geographical areas experienced greater reductions in all-cause mortality than those living in the most deprived areas⁴⁸. Ancestry can influence specific health risks; for example, individuals of South Asian ancestry have a higher genetic predisposition for cardiometabolic diseases than individuals of other ancestries. However, the observed decline in all-cause mortality suggests that environmental and social factors, along with medical advancements, are powerful enough to mitigate some of these baseline ancestral risks over time. Differences in rates of all-cause mortality point to a complex interplay of socioeconomic factors, improved access to healthcare and the healthy migrant effect, which may attenuate over time with increased acculturation^{49,50}.

Our understanding of sequelae of diabetes mellitus has shifted from a narrow focus on traditional complications, such as cardiac, kidney and retinal disease, to a broader view of diabetes mellitus as a systemic driver of diverse chronic conditions. Emerging research increasingly recognizes cancer, dementia and liver disease as major long-term consequences of diabetes mellitus and drivers of diabetes-related mortality. Several studies have noted that cancer is, or is predicted to become, the leading cause of diabetes-related death^{51–53}. Analyses from the UK Biobank, presented at the European Congress on Obesity 2025, suggest that new-onset T2DM is associated with a 48% increased risk of developing obesity-related cancers in men and a 24% increased risk in women, independent of BMI⁵⁴. In addition, T2DM is strongly linked to an increased risk of liver, pancreatic and colorectal cancers, although studies have yet to identify a direct causal relationship^{15,55}. The association is more likely driven by the metabolic features of T2DM

itself, or by an associated trait, such as obesity^{53,56}. Beyond shared risk factors, including obesity, mechanisms such as hyperinsulinaemia, hyperglycaemia and chronic inflammation might play a part to directly promote tumour growth and DNA damage⁵⁷. New findings suggest that certain diabetes medications, particularly GLP1 receptor agonists (GLP1RAs), may reduce the risk of several obesity-associated cancers⁵⁸. This changeover reflects declining cardiovascular disease mortality through improved prevention, coupled with increasing cancer-related mortality, in part reflecting increased cancer incidence secondary to the survival advantage afforded via cardiovascular disease prevention.

Mechanisms/pathophysiology

T2DM arises from complex interactions between genetic predisposition, environmental exposures and progressive cellular dysfunctions. Rather than a uniform disease, T2DM represents a spectrum of inter-related metabolic abnormalities that converge on hyperglycaemia and its complications, many of which are related to excess adiposity as the key aetiological driver. Underlying genetic predisposition and environmental determinants, which remain incompletely characterized, are responsible for various pathophysiological mechanisms that cause T2DM. We propose the 'tumultuous thirteen' framework as a unifying model that integrates these pathophysiological mechanisms underlying the onset, progression and heterogeneity of T2DM (Fig. 3). In this section, we provide state-of-the-art knowledge in key pathogenetic factors among the 'tumultuous thirteen'. Additionally, we also describe other important considerations such as genetic and environmental factors and complications of T2DM.

β-Cell dysfunction

β-Cell failure is central to the onset and progression of T2DM. At diagnosis, individuals have typically lost 40–80% of β-cell function, leading to impaired early and late insulin secretion⁵⁹. This dysfunction arises from

converging mechanisms, including lipotoxicity, glucotoxicity, oxidative and endoplasmic reticulum stress, and mitochondrial impairment. Although β -cells initially stimulate compensatory increases in insulin secretion under insulin-resistant states, sustained metabolic stress ultimately leads to β -cell dysfunction and apoptosis^{60,61}. β -Cell mass is dynamically regulated through a balance of replication, neogenesis and apoptosis^{62,63}.

In cooperation, the quantity and quality of β -cells are essential for glucose homeostasis. The cyclin-dependent kinase (CDK) regulatory network, including CDK4 and CDK6, has a pivotal role in controlling β -cell mass⁶⁴. High-throughput screening studies demonstrate that

harmine-mediated DYRK1A inhibition induces human β -cell replication. This effect is substantially potentiated – reaching replication rates of 15–18% – when combined with inhibition of SMAD and trithorax pathways^{65–67}. Emerging evidence indicates that, under metabolic stress, β -cells may dedifferentiate, which is characterized by loss of mature markers such as PDX1 and MAFA, a process that may be reversible⁶⁸.

Current studies have further elucidated these pathways, expanding our current understanding of the underlying molecular framework. Meteorin-like protein (METRNL), predominantly expressed in β -cells, seems essential for maintaining β -cell identity and compensatory function. One study in mice shows that deletion of *Metrnl* impairs

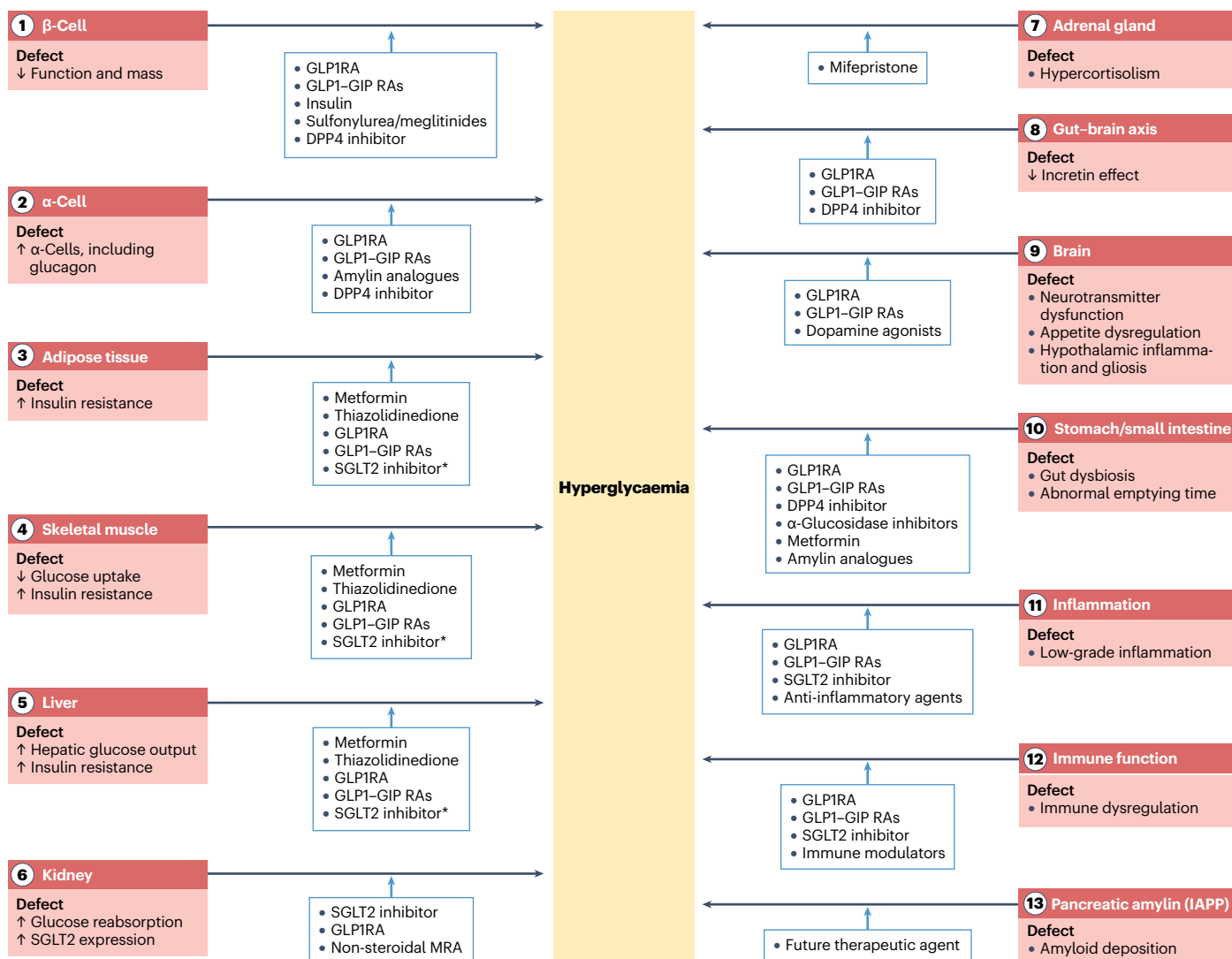


Fig. 3 | Tumultuous thirteen – integrated multi-organ mechanisms and therapeutic targets in T2DM. Type 2 diabetes mellitus (T2DM) arises from 13 interrelated pathophysiological defects spanning endocrine, metabolic, inflammatory and neural systems. Central β -cell failure and α -cell hyperglucagonaemia interact with insulin resistance in adipose tissue, skeletal muscle and liver, together with increased renal glucose reabsorption and impaired incretin action along the gut–brain axis. Additional contributors include adrenal hypercortisolism, hypothalamic neurotransmitter imbalance, gut microbial dysbiosis, chronic low-grade inflammation, immune dysregulation and pancreatic

islet amyloid deposition. These defects form a complex network that sustains hyperglycaemia and metabolic stress. Modern therapies, including GLP1 receptor agonists (GLP1RAs), dual or triple incretin agonists, sodium–glucose co-transporter 2 (SGLT2) inhibitors, thiazolidinediones, metformin, non-steroidal mineralocorticoid receptor antagonists (MRAs) and amylin analogues, act across multiple nodes of this network. Together, they exemplify a shift from glucose-centric control to mechanism-based, multi-organ management of T2DM. DPP4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; IAPP, islet amyloid polypeptide; RA, receptor agonist. *Not the primary mechanism of action.

insulin secretion and promotes a β -to- α transdifferentiation trajectory with downregulation of *Ins1*, *Ins2*, *Pdx1* and *Mafa*⁶⁹. Saturated fatty acid-induced Ca^{2+} overload and prolonged mTORC1 activation impair β -cell autophagy⁷⁰, a protective mechanism against β -cell degeneration and glucose dysregulation⁷¹. Another study showed that pancreatic fibrosis, identified by CT and confirmed in UK Biobank MRI data, was associated with deterioration of β -cell function⁷². Conversely, caloric restriction, weight loss and glycaemic control can partially restore β -cell identity in animal models and humans, highlighting the potential reversibility of early β -cell dysfunction^{73,74}.

Insulin resistance

Insulin resistance, a hallmark of T2DM, affects liver, skeletal muscle and adipose tissue, with each organ contributing uniquely to metabolic dysregulation⁷⁵. Although reduced insulin responsiveness can initially reflect an adaptive response to nutrient excess^{75–78}, chronic overnutrition transforms this response into a maladaptive state that disrupts endocrine signalling, lipid handling and glucose homeostasis.

Adipose tissue insulin resistance and adipocyte dysfunction. Adipose tissue insulin resistance constitutes a key pathophysiological hallmark in T2DM and the metabolic syndrome^{75,79}. Nutrient overload activates NF- κ B, JNK and endoplasmic reticulum stress pathways, impairing proximal insulin signalling and promoting the recruitment of pro-inflammatory macrophages^{77,80}. This inflammatory microenvironment in turn amplifies cytokine production, reduces adiponectin and alters the adipokine milieu⁷⁸, reinforcing systemic insulin resistance. When adipocytes no longer have the ability to safely store lipids, the resultant increased release of free fatty acids promotes hepatic gluconeogenesis, ectopic lipid accumulation in muscle and liver, and impaired glucose uptake in peripheral tissues⁸¹. Thus, dysfunctional adipose tissue contributes directly to multi-organ insulin resistance and systemic metabolic deterioration.

Skeletal muscle insulin resistance and reduced glucose uptake. Skeletal muscle accounts for the utilization of the majority of postprandial glucose⁸², making skeletal muscle insulin resistance a major determinant of systemic glycaemic control. High-quality muscle – with preserved oxidative capacity and minimal lipid infiltration – supports whole-body insulin sensitivity, whereas myosteatosis predisposes individuals to insulin resistance and cardiometabolic disease^{83,84}. Intramuscular lipid accumulation correlates with reduced strength and physical performance⁸⁵, glucose dysregulation⁸⁶ and cardiovascular events⁸⁷. Mechanistic studies using ¹H-magnetic resonance spectroscopy show that intramyocellular lipid disrupts insulin signalling via diacylglycerol- $\text{PKC}\theta$ activation, mitochondrial stress and impaired oxidative flux, contributing to metabolic inflexibility^{88,89}. Nevertheless, muscle lipid content is modifiable: caloric restriction reduces intramuscular fat and improves insulin sensitivity⁹⁰, whereas limb disuse leads to rapid increases in fat infiltration and decreases strength⁹¹.

Hepatic insulin resistance and MASLD. The liver integrates hormonal, inflammatory and nutrient signals to regulate glucose homeostasis. Hepatic insulin resistance – characterized by impaired suppression of gluconeogenesis despite hyperinsulinaemia – drives fasting and post-absorptive hyperglycaemia in T2DM⁹².

Intrahepatic lipid accumulation is a major contributor to insulin resistance – diacylglycerol-mediated activation of $\text{PKC}\epsilon$ impairs IRS-PI3K-AKT-FOXO1 signalling and maintains expression of G6PC and PCK1 (refs. 76,93,94). Additional contributors include altered

mitochondrial redox state, oxidative stress, inflammation and endoplasmic reticulum stress^{95–97}. Selective hepatic insulin resistance represents a key conceptual advancement in T2DM, whereby hyperinsulinaemia preferentially reduces IRS2 in periportal hepatocytes – impairing the anti-gluconeogenic action of insulin – at the same time preserving IRS1 in perivenous hepatocytes, sustaining SREBP1c-mediated lipogenesis^{98,99}. This zoned imbalance explains the coexistence of hyperglycaemia and steatosis in T2DM.

The updated nomenclature to MASLD (formerly termed non-alcoholic fatty liver disease) reflects its role as a hepatic manifestation of systemic cardiometabolic dysfunction¹⁰⁰. MASLD requires the presence of metabolic impairment – dysglycaemia, adipose dysfunction or insulin resistance – together with steatosis¹⁰¹. With a global prevalence approaching 30–38%, MASLD increases the risks of cardiovascular disease, cirrhosis, hepatocellular carcinoma and liver-related mortality¹⁰².

Incretin biology

The incretin hormones GLP1 and glucose-dependent insulinotropic polypeptide (GIP) potentiate insulin secretion in response to oral glucose, accounting for up to 70% of postprandial insulin release – in people with T2DM, incretin function is impaired⁶¹. Although GLP1 levels may be preserved early in the disease, the efficacy of GLP1 diminishes over time. In addition, GIP becomes less effective at stimulating insulin secretion with disease progression, especially in individuals with obesity or T2DM. Beyond islet effects, incretins regulate appetite, gastric motility, cardiovascular tone and renal sodium handling¹⁰³. These pleiotropic actions underlie the success of GLP1-based therapies in improving glucose control and promoting weight loss.

Gut dysbiosis

Gut dysbiosis, that is, the imbalance in gut microbial composition, may contribute to the development of insulin resistance and T2DM, although the strength of causal evidence in humans remains limited. Individuals with T2DM often exhibit reduced abundance of beneficial microbes such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*¹⁰⁴, along with enrichment of potentially harmful species, including *Intestinibacter bartlettii*¹⁰⁵ and *Enterococcus faecalis*¹⁰⁶. Studies have shown a link between altered microbial metabolism and impaired host metabolic regulation. For instance, short-chain fatty acids, such as butyrate and propionate, enhance intestinal barrier function, stimulate GLP1 secretion and improve insulin sensitivity¹⁰⁴, whereas elevated levels of trimethylamine-*N*-oxide and branched-chain amino acids have been associated with inflammation, insulin resistance and elevated cardiovascular risk in T2DM¹⁰⁷.

Gut-derived secondary bile acids and tryptophan metabolites also modulate glucose metabolism and host immunity via FXR, TGR5 and aryl hydrocarbon receptor signalling^{104,107}. Collectively, these findings suggest that gut dysbiosis and altered microbially derived metabolites may exacerbate insulin resistance and contribute to β -cell stress in susceptible individuals. Certain glucose-lowering medications, including metformin and GLP1RAs, have been shown to modify microbial composition or function, raising the possibility that microbiome modulation may partly mediate their metabolic benefits (Fig. 4).

Hypercortisolism

Hypercortisolism is increasingly recognized as a contributor to poor glycaemic control in a subset of individuals with difficult-to-control T2DM. A study using a dexamethasone suppression test, which involves

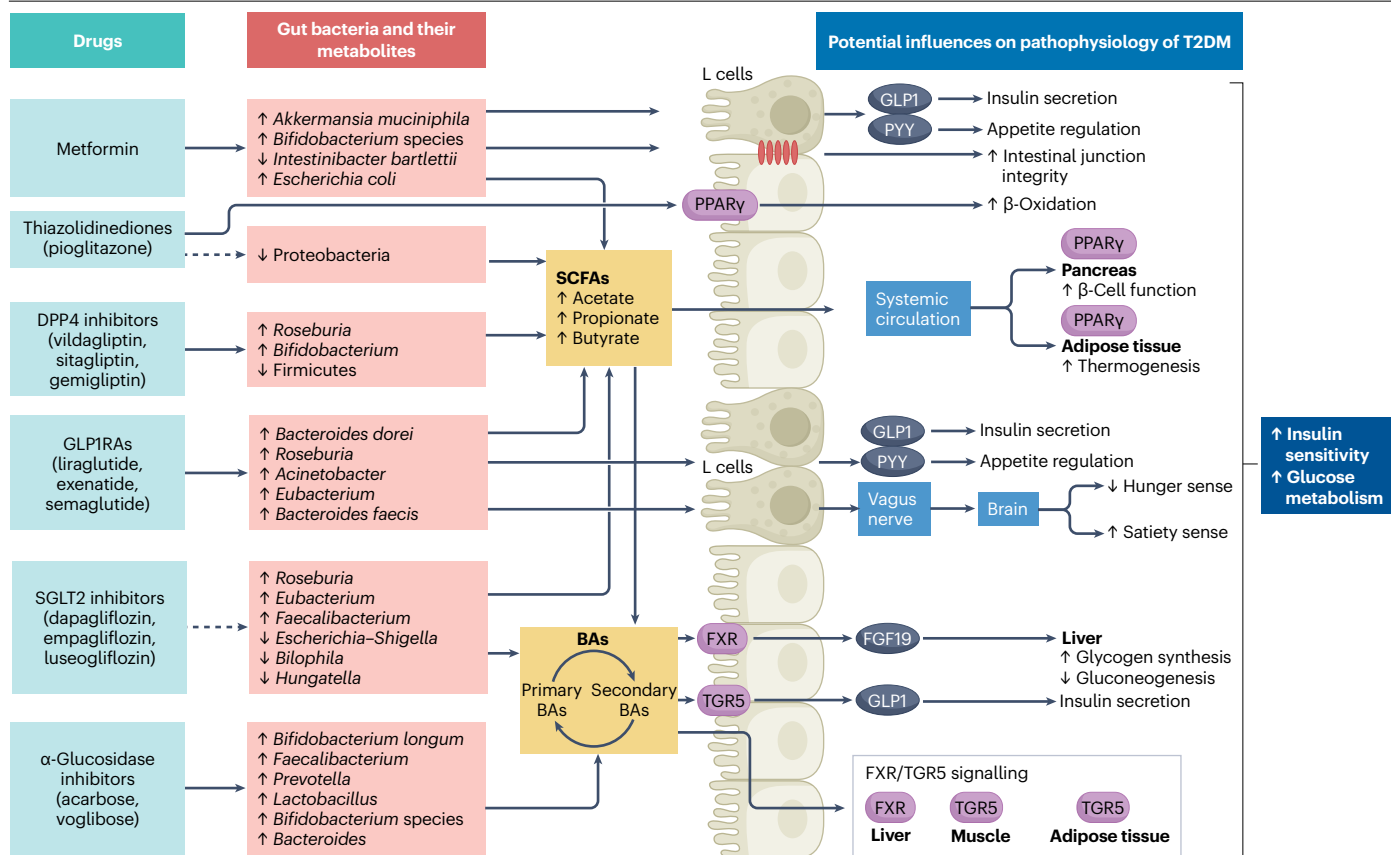


Fig. 4 | Potential interactions between glucose-lowering therapies, the gut microbiome and host glucose metabolism. Several glucose-lowering agents have been reported to modify gut microbial composition or microbial metabolite profiles, which may contribute to their metabolic effects in type 2 diabetes mellitus (T2DM). Metformin increases the abundance of taxa such as *Akkermansia muciniphila* and *Bifidobacterium* and reduces *Intestinibacter bartlettii*, changes that have been associated with increased production of short-chain fatty acids (SCFAs), including acetate, propionate and butyrate. SCFAs support epithelial barrier integrity, influence GLP1 secretion and may enhance insulin sensitivity. Other drug classes, including thiazolidinediones, dipeptidyl peptidase 4 (DPP4) inhibitors and GLP1 receptor agonists (GLP1RAs), have

been reported to shift microbial communities towards SCFA-producing genera (for example, *Roseburia*, *Eubacterium*) and to alter bile acid (BA) pools, thereby influencing FXR and TGR5 signalling pathways. These pathways can modulate enteroendocrine hormone secretion (GLP1 and peptide YY (PYY)) and FGF19, with downstream effects on hepatic metabolism, appetite regulation and energy balance. Sodium-glucose co-transporter 2 (SGLT2) inhibitors and α-glucosidase inhibitors have also been linked to changes in microbial fermentation and BA metabolism. Overall, these microbiome–drug interactions remain incompletely defined but may represent one mechanism, among several, through which glucose-lowering therapies exert metabolic benefits.

administration of a steroid (dexamethasone) to assess whether cortisol secretion by the adrenal gland can be suppressed, has reported biochemical non-suppression in up to 25% of such individuals¹⁰⁸, indicating excess cortisol secretion. Excess glucocorticoid signalling disrupts metabolic regulation by increasing hepatic glucose production, inducing insulin resistance in skeletal muscle and adipose tissue, enhancing lipolysis and ectopic lipid deposition, and impairing β-cell function and incretin responsiveness¹⁰⁹. In the CATALYST study, glucocorticoid receptor antagonism with mifepristone improved HbA1c and reduced body weight in individuals with difficult-to-control T2DM and biochemical hypercortisolism⁵². However, further studies are needed to identify those most likely to benefit from targeted intervention.

Genetic and environmental factors

Upstream of the tumultuous thirteen, genetic and environmental factors underpin the tumultuous thirteen mechanisms. Genetic predisposition

plays a central part in T2DM, with >600 independent loci identified across ancestries through large-scale genome-wide association studies (GWAS) contributing to polygenic risk¹¹⁰. Most risk variants are found in non-coding regions and affect gene regulatory networks that are functional in pancreatic islets, pointing to β-cell dysfunction as the primary mechanism of genetic susceptibility¹¹⁰. Notably, variants in loci such as *TCF7L2*, *KCNQ1* and *HNF1A* influence islet development, glucose-stimulated insulin secretion and pro-insulin processing. Fine-mapping and single-cell epigenomic data have revealed cell-type-specific regulatory effects, showing that distinct islet cell subtypes, particularly β-cells and α-cells, contribute to disease risk in a context-dependent manner^{110,111}. Although common variants have modest individual effects and collectively explain ~20% of T2DM heritability, rare coding variants in key developmental and β-cell transcription factor genes, such as *GLIS3*, *PDX1*, *NEUROD1* and *RFX6*, highlight essential pathways regulating β-cell formation, survival and function^{110,111}. By contrast, the most prevalent monogenic forms involve

GCK and *HNFA1A*, accounting for the most common type of monogenic diabetes, known as maturity-onset diabetes of the young – a separate disease entity to T2DM. These variants provide insight into glucose sensing and insulin secretory regulation¹¹². Intriguingly, shared genetic architecture links T2DM with related traits, such as BMI and lipid metabolism, with pleiotropic loci (for example, *MC4R*, *GCKR* and *FTO*) pointing to convergent pathways in energy balance, insulin secretion and metabolic regulation in the liver, which explains the frequent clustering of these cardiometabolic conditions^{110,111}. Environmental exposures modulate genetic risk throughout life. Overnutrition, physical inactivity, intrauterine growth restriction and exposure to endocrine-disrupting chemicals alter chromatin accessibility, DNA methylation and transcriptional responses in tissues involved in metabolism¹¹³. These gene–environment interactions contribute to variable phenotypes across different populations. Independent of genetics, many environmental risk factors are likely to have a causal role in the development of T2DM upstream of the tumultuous thirteen mechanisms. As discussed, the importance of the social determinants of health in influencing these modifiable causal factors cannot be overstated.

T2DM-associated complications

T2DM is associated with a multitude of complications. Traditionally, complications of diabetes mellitus have been categorized into microvascular (for example, nephropathy, neuropathy and retinopathy) and macrovascular (for example, coronary artery disease, cerebrovascular disease and peripheral artery disease). Given the well-established causal link between obesity and T2DM, individuals with T2DM are also at increased risk of developing obesity-associated complications, including metabolic dysfunction-associated steatohepatitis (MASH) and/or MASLD, obstructive sleep apnoea, osteoarthritis, heart failure and obesity-related cancer. Hyperglycaemia and excess adiposity constitute the main drivers of mechanisms underlying the complications of T2DM (Fig. 5). Several studies have also described the psychological and social consequences of T2DM^{114,115}.

Hyperglycaemia and complications. Chronic hyperglycaemia is a key factor underlying the development of diabetic complications through metabolic, inflammatory and haemodynamic mechanisms. Excess glucose induces oxidative stress, advanced glycation end product formation, PKC activation and mitochondrial dysfunction, which collectively impair endothelial function and disrupt interorgan communication^{116,117}.

In microvascular tissues, these shared pathways produce interrelated manifestations. In the retina, oxidative injury and basement membrane thickening lead to capillary loss and neovascularization¹¹⁸. In the kidney, glomerular hyperfiltration, mesangial expansion and podocyte injury progress to fibrosis, accompanied by activation of NF- κ B, JAK–STAT signalling pathways and other inflammatory networks across nephron compartments¹¹⁹. Diabetic neuropathy similarly demonstrates convergent mechanisms, including polyol-pathway flux, mitochondrial dysfunction and cytokine-mediated axonal injury¹²⁰.

Macrovascular disease associated with diabetes mellitus represents a systemic extension of these processes. Hyperglycaemia, insulin resistance, dyslipidaemia and chronic inflammation accelerate atherosclerosis by promoting endothelial activation, leukocyte adhesion and vascular smooth-muscle cell proliferation^{121–124}. Circulating inflammatory cytokines, such as IL-6, TNF and CRP, contribute to vascular remodelling and predict cardiovascular and renal risk^{122,123}.

Acute consequences of marked hyperglycaemia also warrant consideration. Osmotic diuresis causes polyuria, polydipsia and

dehydration, which in severe cases can progress to diabetic ketoacidosis (DKA) or a hyperosmolar hyperglycaemic state (HHS). DKA results from severe insulin deficiency, leading to unchecked ketogenesis and metabolic acidosis, whereas HHS is characterized by extreme hyperglycaemia, hyperosmolality and profound dehydration with minimal ketosis¹²⁵. One review reported that HHS accounts for up to 8–10% of hyperglycaemic crises in adults with T2DM and carries higher mortality than DKA, reflecting cardiovascular, renal and central nervous system vulnerability¹²⁵. Together, hyperglycaemia orchestrates a network of cellular stress and inflammatory responses that link microvascular and macrovascular pathology through common biological pathways.

Excess adiposity and complications. Excess adiposity is a key pathophysiological driver of T2DM and related cardiovascular risk factors, including hypertension, dyslipidaemia, MASLD and chronic low-grade inflammation, and contributes to comorbidities in T2DM primarily through adipose tissue dysfunction rather than through overall fat mass alone. When subcutaneous adipose tissue reaches its storage limit, adipocyte hypertrophy and inflammation develop, promoting lipid spillover, systemic insulin resistance and ectopic fat deposition¹²⁶. Through these processes, surplus lipids are redirected towards organs that are poorly equipped for lipid handling, thereby imposing metabolic stress and promoting multi-organ dysfunction.

Multiple pathogenic pathways link dysfunctional adipose tissue to complications of T2DM, including lipotoxicity, oxidative stress, and systemic and local inflammation¹²⁷, with emerging evidence also implicating hypothalamic inflammatory signalling¹²⁸. Visceral adipose tissue is particularly harmful owing to its heightened lipolytic activity and secretion of pro-inflammatory adipokines, which exacerbate hepatic insulin resistance, endothelial dysfunction and atherogenesis¹²⁷. Consistent findings from metabolic imaging and large population studies show that visceral and ectopic fat, rather than BMI, best predict dysglycaemia, atherogenic lipid profiles and cardiovascular disease^{129,130}.

Ectopic lipid accumulation further amplifies cardiometabolic risk through organ-specific mechanisms. Pancreatic fat impairs insulin secretion by β -cells¹³¹; hepatic fat is pathognomonic of steatohepatitis and associated with hepatic insulin resistance and hepatokine release¹³²; intramuscular fat reduces oxidative capacity and glucose uptake; and pericardial and perivascular fat promote local vascular inflammation and accelerate atherosclerosis¹³³.

Cellular overnutrition resulting from chronic excess caloric intake induces pathological processes that are not solely determined by the absolute amount of ectopic lipid deposition. When physiological energy storage capacity is exceeded, cells accumulate bioactive lipid intermediates – most notably diacylglycerols and ceramides – which disrupt insulin signalling via activation of PKC isoforms and inhibition of insulin receptor substrate pathways, thereby promoting insulin resistance and inflammation^{134,135}. In parallel, sustained nutrient overload drives mitochondrial maladaptation, characterized by impaired oxidative flexibility, incomplete fatty acid oxidation and increased generation of reactive oxygen species, further amplifying cellular stress responses^{76,96,136–138}. These interrelated mechanisms are particularly relevant in the liver, where lipotoxic signalling and mitochondrial dysfunction contribute to hepatic insulin resistance and the progression of MASLD^{139,140}.

In addition, therapeutic evidence reinforces these mechanisms. Weight-loss interventions, including GLP1RAs and metabolic surgery, consistently reduce visceral and ectopic fat and improve cardiometabolic outcomes in T2DM^{16,126,141–145}. Collectively, these data demonstrate

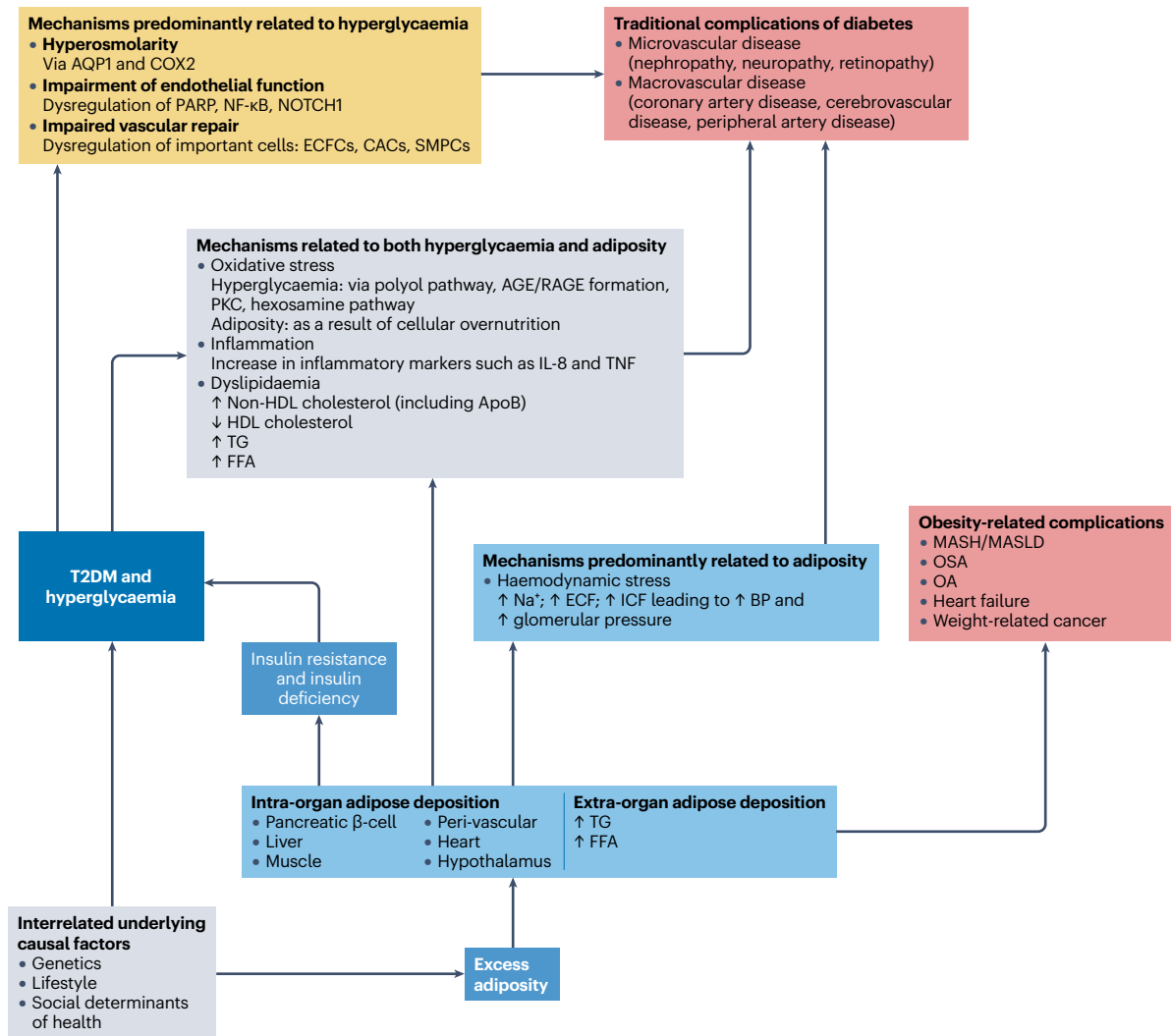


Fig. 5 | Potential mechanisms of complications in individuals with T2DM. Genetic, lifestyle and social factors cause both adiposity and type 2 diabetes mellitus (T2DM). While there are associations with these factors and both conditions independently, excess adiposity also contributes to the development of T2DM, hyperglycaemia and its complications through several mechanisms¹¹⁸. This risk is potentially mediated through intra-organ adipose deposition, which ultimately impairs organ function. Excess adiposity also leads to dyslipidaemia, intracellular overnutrition and subsequent inflammation and oxidative stress, and haemodynamic stress. Through these mechanisms, excess adiposity leads to both the traditional complications of T2DM (microvascular and macrovascular disease) and obesity-related complications. T2DM and hyperglycaemia also contribute to complications via numerous pathways,

including via hyperosmolarity, impairment of endothelial function, impairment of vascular repair, vascular damage, oxidative stress and inflammation¹⁰⁸. ApoB, apolipoprotein B; AQP1, aquaporin 1; BP, blood pressure; CACs, circulating angiogenic cells; COX2, cyclooxygenase 2; ECF, extracellular fluid; ECFCs, endothelial colony-forming cells; FFA, free fatty acid; HDL, high-density lipoprotein; ICF, intracellular fluid; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NF-κB, nuclear factor-κB; OA, osteoarthritis; OSA, obstructive sleep apnoea; PARP, poly(ADP-ribose) polymerase; PKC, protein kinase C; RAGE/AGE, receptor for advanced glycation end products/advanced glycation end products; SMPCs, smooth-muscle progenitor cells; TG, triglyceride; TNF, tumour necrosis factor.

that adipose distribution and tissue function – rather than body weight alone – are the major determinants of metabolic risk in T2DM.

Diagnosis, screening and prevention

Diagnosis

T2DM can be diagnosed based on plasma glucose criteria – fasting plasma glucose, 1-h or 2-h plasma glucose during an oral glucose tolerance test, or random glucose measurements when hyperglycaemic

symptoms are present or by HbA1c¹⁴⁶. However, compared with fasting plasma glucose and HbA1c cut points, the 2-h plasma glucose value leads to more people being diagnosed with prediabetes and diabetes mellitus¹⁴⁷ (Supplementary Fig. 1).

Although T2DM is the most common type of diabetes, distinguishing T2DM from other types of diabetes can be challenging at diagnosis, particularly type 1 diabetes mellitus (T1DM) (Fig. 6). Numerous clinical features are associated with T1DM; however, no single feature

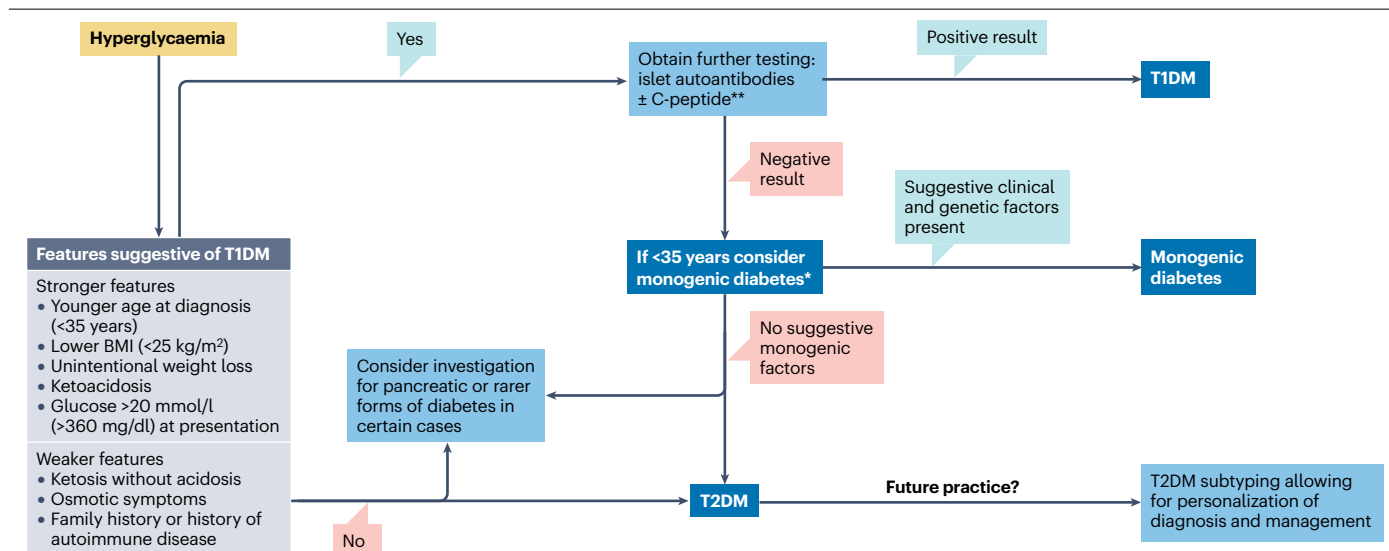


Fig. 6 | The diagnosis of T2DM. An overview of consensus diagnostic algorithm for type 1 diabetes mellitus (T1DM) versus type 2 diabetes mellitus (T2DM)¹³⁹. If features of T1DM are present, definitive testing should be sought, including islet autoantibodies with or without C-peptide testing. If features of T1DM and rarer forms of diabetes are absent, then T2DM can be diagnosed. *Features of monogenic diabetes: HbA1c <58 mmol/mol (7.5%) at diagnosis, one parent

with monogenic diabetes, features of specific monogenic cause (for example, renal cysts, partial lipodystrophy, maternally inherited deafness, severe insulin resistance in the absence of obesity) and monogenic diabetes prediction model probability >5%. **Plasma C-peptide is preferred method when available, but urinary C-peptide is also acceptable.

can be used to differentiate diabetes type. Nevertheless, younger age at diagnosis and early insulin requirement are the strongest predictive clinical features¹⁴⁸. Ongoing robust insulin production several years after diagnosis makes T1DM less likely; however, studies have shown that some individuals with T1DM may continue to produce small amounts of endogenous insulin even decades after diagnosis¹⁴⁸. An assessment of islet autoantibodies with a random urinary analysis or plasma C-peptide measurement (with concurrent glucose) within 5 h of eating beyond 3 years after diagnosis is advised when the diabetes type is uncertain¹⁴⁸. Adult-onset T1DM makes diagnosis more challenging owing to the often slower progression to insulin deficiency, and is frequently misdiagnosed as T2DM for years, or as some other forms of diabetes mellitus, including maturity-onset diabetes of the young, pancreatogenic diabetes (type 3c), cystic fibrosis-related diabetes mellitus and malnutrition-associated diabetes mellitus^{149,150}.

T2DM is a highly heterogeneous disease with respect to both the genetic and phenotypic characteristics, with much research focused on the validity of subclassification of T2DM. Although GWAS have conventionally focused on European ancestry cohorts, limiting global generalizability^{110,151}, newer multi-ancestry analyses have identified distinct genetic clusters associated with different cardiometabolic profiles¹⁵². These clusters vary in distribution across ancestry groups and help explain differences in T2DM risk at reduced BMI thresholds, particularly among East Asian populations, highlighting the role of genetic architecture in shaping ancestry-specific disease risk. Unlike biomarkers that are variable over time, germline genetic markers do not change with disease progression or treatment¹⁵³. The increasing availability of diverse biobanks has enabled multi-ancestry GWAS to enhance the discovery of genetic variants across diabetes types¹⁵⁴, and classification of individuals with T2DM by these genetic pathways may offer a step towards genetically informed T2DM diagnosis and management.

Progress has been made towards subclassification of T2DM based on phenotypic traits, with potential implications for disease progression and risk of complications. T2DM presents with highly variable clinical features, which can include characteristics reflecting more insulin-resistant versus insulin-deficient disease profiles and milder or diet-controlled disease versus rapidly progressive fulminant disease; however, currently, all individuals receive the same diagnosis¹⁵⁵. A novel classification of diabetes mellitus based on data-driven cluster analysis of six commonly measured variables has identified four subtypes of T2DM (Table 1) – severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes, mild obesity-related diabetes and mild age-related diabetes¹⁵⁶. People with SIDD have an increased prevalence of diabetic retinopathy, sensorimotor polyneuropathy and cardiac autonomic neuropathy at diagnosis and progress more rapidly to insulin treatment, whereas people with severe insulin-resistant diabetes are at increased risk for chronic kidney disease and MASLD¹⁵⁷. These T2DM subtypes have been replicated and cross-validated in various populations and seem to be dependent on factors such as distribution of ancestry, age, duration of T2DM and BMI^{158–160}. For example, SIDD is the dominant subtype in Indian populations, whereas mild age-related diabetes is the dominant subtype in European populations^{157,161} (Table 1). Other data suggest that heterogeneity in T2DM occurs on a continuum, and algorithms that reflect this on a continuous scale may be more useful for targeted prevention and precision medicine than discrete subclassification categories¹⁶².

However, subclassification of T2DM is not currently in widespread clinical use. Factors that determine clustering at diagnosis may change over time, implying that people can transition between clusters, limiting their application for long-term prognosis and treatment planning. Furthermore, simple clinical characteristics may be more useful for prognostication than subclassification categories¹⁶³. Regardless, further classification of people with T2DM is an important first step in the shift towards offering personalized medicine approaches.

Screening

Globally, a consistently high proportion of individuals (~40%) have undiagnosed T2DM². Screening can identify individuals with undiagnosed diabetes and identify individuals with prediabetes who can benefit from preventative interventions. Screening should start with an assessment of risk factors, often aided by the use of assessment tools, such as FINDRISC, ADA Diabetes Risk Test and Leicester Risk Assessment Score^{164–166}, followed by laboratory screening for people identified as having a high risk, using fasting plasma glucose, 30-min plasma glucose and HbA1c. Combined measurement of fasting plasma glucose and HbA1c may be useful¹⁶⁷, and while 2-h plasma glucose has been traditionally used, the 1-h plasma glucose has also been advocated as another option¹⁴⁷.

Ethnicity is well established to influence the risk of T2DM, driven by substantial genetic risk¹⁵² and exacerbated by a number of environmental factors and social determinants of health³⁵. Although people of Asian ethnicity have low BMI, they seem to have more subcutaneous fat and different fat distributions, with more upper body fat than people of white ethnicity, with differences exacerbated in females¹⁶⁸. Studies have shown equivalent T2DM risk in a European subpopulation at a BMI of 30 kg/m² and in an East Asian subpopulation at a BMI of 24.2 kg/m² (22.9–25.5 kg/m²)¹⁶⁸. After adjusting for cluster-specific genetic risk, the equivalent BMI threshold increased to 28.5 kg/m² (27.1–30.0 kg/m²) in the East Asian group. Hence, using risk factor screening thresholds (that is, BMI) specific to race or ethnicity can help to reduce disparities in T2DM diagnosis in South Asian, African-Caribbean and Hispanic American individuals, who develop T2DM at a younger age and lower BMI than people of white ethnicity^{169,170}.

Prevention

Timely intervention in individuals at high risk plays a vital part in delaying or preventing the development of T2DM. Taking the broader societal, community and local environment factors into consideration is of paramount importance when planning T2DM preventive measures (Fig. 2). Strategies for diabetes mellitus prevention can be broadly categorized into the overarching tiers of population-level (upstream) and individual-level (downstream) approaches. Population-level approaches aim to tackle the upstream societal determinants of unhealthy diets, sedentary behaviour and obesity¹⁷¹ via mechanisms including the reformulation of foods (for example, by reducing the sugar content), provision of information (for example, food labelling), fiscal measures (such as taxes on less-healthy food products), or structural and environmental measures (for example, new infrastructure for active commuting such as cycle lanes)¹⁷¹.

Individual-level approaches to diabetes prevention focus on identifying people at the highest risk of developing T2DM and offering targeted interventions. Diabetes prevention programmes that centre around structured lifestyle modifications (that is, dietary modifications and physical exercise), including the Diabetes Prevention Programme in the USA¹⁷², the Finnish Diabetes Prevention study¹⁶⁶ and the Da Qing Diabetes Prevention Outcome study in China¹⁷³, have been effective at preventing or delaying progression of T2DM in people with impaired glucose tolerance and have demonstrated sustained long-term effects^{172,174}. Weight loss of 5–7% can reduce the risk of developing T2DM^{173,175}, with greater benefits shown with 7–10% weight loss¹⁷⁶. Modifications to specific lifestyle components, such as sleep, may also have an effect on the progression to T2DM. Both long and short sleep duration, poor sleep quality and evening chronotype are well established to be associated with an increased risk of T2DM^{177,178}.

In addition to the largely lifestyle-focused prevention programmes, pharmacotherapies are also shown to prevent or delay T2DM (for example, metformin, α -glucosidase inhibitors, GLP1-based therapies and thiazolidinediones). For example, studies have shown that metformin therapy reduces the risk of T2DM by 31%¹⁷⁵, and tirzepatide is associated with a 93% lower risk of progression to T2DM than placebo over a 176-week period in individuals with prediabetes and obesity¹⁷⁹. Although no pharmacological agent has been approved by the FDA for T2DM prevention, the wealth of observational, mechanistic and clinical trial data in support of the efficacy and cost-effectiveness of metformin for T2DM prevention in individuals at high risk has resulted in its use being included in guideline recommendations in many countries.

Remission

Remission of T2DM is currently defined as HbA1c below the diagnostic threshold of 6.5% (48 mmol/mol) without the use of glucose-lowering medications within at least 3 months¹⁸⁰. The exclusion of glucose-lowering medications from the definition distinguishes T2DM remission from the definition used in other diseases. However, whether the remission definition could be broadened to include individuals who achieve euglycaemia while using glucose-lowering medication is an ongoing debate, as evidence is lacking that achieving euglycaemia without glucose-lowering medications is more beneficial than with them¹⁸¹. Weight loss and increased β -cell function are the main determinants of T2DM remission, whereas the main drivers of prediabetes remission are improvement of insulin sensitivity and reduction of visceral adipose tissue^{180,182}. A robust dose–response relationship between

Table 1 | Possible subtypes of T2DM

Subtype	Common features	Proportion of T2DM cases in Sweden (ANDIS) (%) ^{a142}	Proportion of T2DM cases in India (WellGen) (%) ¹⁴⁵
Severe insulin-deficient diabetes	Low BMI Younger age at onset Severe β -cell dysfunction Low insulin resistance High HbA1c High risk of complications	19	53
Mild age-related diabetes	Normal to slightly elevated BMI Older age at onset Mild β -cell dysfunction Low insulin resistance Low risk of complications	41	8
Mild obesity-related diabetes	High BMI Younger age at onset Insulin resistance Preserved β -cell function Moderate HbA1c	23	38
Severe insulin-resistant diabetes	High BMI Older age at onset Severe insulin resistance Preserved β -cell function High risk of complications	16	1

T2DM, type 2 diabetes mellitus. ^aPercentages recalculated excluding 6% of original sample with autoimmune diabetes to allow comparison with India (WellGen) data.

weight loss and diabetes remission has been observed, independent of age, diabetes duration, HbA1c, BMI and type of intervention¹⁸³. Remission has been proposed as a key therapeutic goal in the management of T2DM¹⁸⁴.

Management

The goal of care for people with T2DM is to improve their quality of life while simultaneously decreasing the risk of diabetes-related complications. Key objectives of T2DM management include achieving individualized glycaemic targets to prevent or delay microvascular complications while avoiding hypoglycaemia; weight management, as excess body weight, particularly visceral fat, plays a central part in the development and progression of insulin resistance and β -cell dysfunction; reduction of cardiovascular risk via comprehensive risk factor modification and appropriate use of medications with proven cardiovascular and renal benefits; prioritizing psychosocial well-being as a desired outcome to improve quality of life; and highlighting the importance of the 24-h physical behaviours²⁰. Weight loss can considerably improve glycaemic control, reduce disease progression and the need for glucose-lowering medications, and contribute to improvements in cardiovascular risk factors (blood pressure, lipids and inflammation), thereby reducing the risk of cardiovascular disease. The importance of integrating early glycaemic control as a treatment goal in the hierarchy of diabetes management has been emphasized alongside multifactorial management using a multidisciplinary approach¹⁸⁵.

Lifestyle modifications, including healthy eating and physical activity, are fundamental in managing T2DM. Importantly, care should be tailored according to the person's age, comorbidities, preferences and social circumstances. Regular monitoring, shared decision-making and attention to mental health and diabetes distress are integral components. Ultimately, the goal is to empower individuals to manage their condition effectively, minimize disease burden and maintain functional independence and well-being.

Diabetes self-management education and support

Diabetes self-management education and support (DSMES) should form an integral basis of any T2DM management plan that is developmentally appropriate and culturally sensitive^{20,186}. Traditionally involving face-to-face sessions (individual or group-based), the purpose of DSMES is to facilitate informed decision-making and problem-solving, optimize self-care behaviours and ultimately empower people to manage living with T2DM¹⁸⁷, aligning with the model of holistic and person-centred care. DSMES programmes should be established on theory and based on evidence¹⁸⁸. Delivery models can include cost-effective and culturally adapted peer- or community health worker-led sessions when appropriately trained and linked with clinical oversight. Such approaches are effective at improving knowledge, confidence, HbA1c levels, psychosocial well-being and behavioural outcomes^{189–192}.

Widescale use of digital DSMES programmes has increased exponentially as a convenient and cost-effective alternative to traditional modes of delivery¹⁹³. While demonstrating high levels of engagement and retention¹⁹⁴, digital DSMES interventions can be effective at improving HbA1c levels^{195,196}, possibly to a greater extent than those observed with conventional face-to-face delivery methods¹⁹⁷. Notably, selecting the optimal mode of delivery for DSMES comes down to individual preferences and circumstances.

Self-care recommendations should align with the person's capacity, including physical and psychological factors¹⁹⁸. The person's capacity for self-care may be assessed by reviewing the individual biology,

resources, environment, self-care workload and social support¹⁹⁹. The interactions between these factors are pivotal in person-centred diabetes care²⁰⁰.

Lifestyle modification

Lifestyle modification is the mainstay of T2DM prevention and management, including physical activity behaviours, nutrition therapy and weight management. In 2022, the American Diabetes Association and European Association for the Study of Diabetes consensus report highlighted the importance of the 24-h physical behaviours for people living with T2DM²⁰ and coined the term, 'the five Ss' (sleep, sitting, stepping, sweating and strengthening) (Fig. 7). Alterations to these lifestyle factors considerably impact cardiometabolic health, psychosocial well-being and weight management in T2DM¹⁴³.

Physical activity. Regular aerobic and resistance exercise is recommended for all adults living with T2DM, with a target of ≥ 150 min per week of moderate-intensity activity, or ≥ 75 min per week of vigorous-intensity activity for those able to tolerate it (Table 2). Resistance training is also recommended two to three times per week given the increased risk of impaired physical function and frailty in this population¹⁸⁷ and the loss of lean mass associated with some glucose-lowering medications²⁰¹. Specifically, T2DM represents a model of accelerated biological ageing²⁰, within which individuals are at increased risk of frailty and impaired physical function in the presence of obesity²⁰². While the concept of frailty has traditionally been considered exclusively in the context of older adults, the frailty phenotype in T2DM can coexist in younger persons with underlying obesity and multiple comorbidities²⁰².

Structured exercise interventions of at least 8 weeks have been shown to reduce HbA1c by 0.6–0.7%, even in the absence of substantial weight loss²⁰³. Even modest increases in daily activity, such as an additional 500 steps per day, are associated with reduced cardiovascular morbidity and all-cause mortality^{204,205}. Breaking up prolonged sedentary time with light activity also confers metabolic benefits²⁰⁶.

Sleep. Sleep is now recognized as a key lifestyle factor in diabetes mellitus management. Both short (<6 h) and long (>9 h) sleep durations are associated with increased risk of T2DM, with optimal risk reduction at ~7 h of sleep per night¹⁷⁷. Poor sleep quality and evening chronotype are also independently associated with increased T2DM risk and progression. Addressing sleep duration, quality and timing should be integrated into comprehensive diabetes care¹⁷⁷.

Diet. Dietary interventions are a key component of diabetes management. Nutrition regimens incorporating low carbohydrate intakes, foods with low glycaemic index, and Mediterranean, vegetarian and high-protein diets have all been shown to be effective^{207–209}, with the Mediterranean diet particularly having robust evidence¹⁰⁵. However, the evidence for one type of macronutrient profile over others is less convincing than that for hypocaloric diets in general²¹⁰. Specifically, any diet that aids weight loss is likely to be effective in promoting glycaemic control and reducing cardiovascular risk. This concept is well evidenced with the approaches to very-low-energy diets, including the use of meal replacement products, which have been successfully deployed to achieve T2DM remission²¹⁰.

Although the short-term effectiveness of lifestyle interventions in the management of T2DM is well documented²¹¹, their effective implementation²¹² and long-term sustainability are limited by

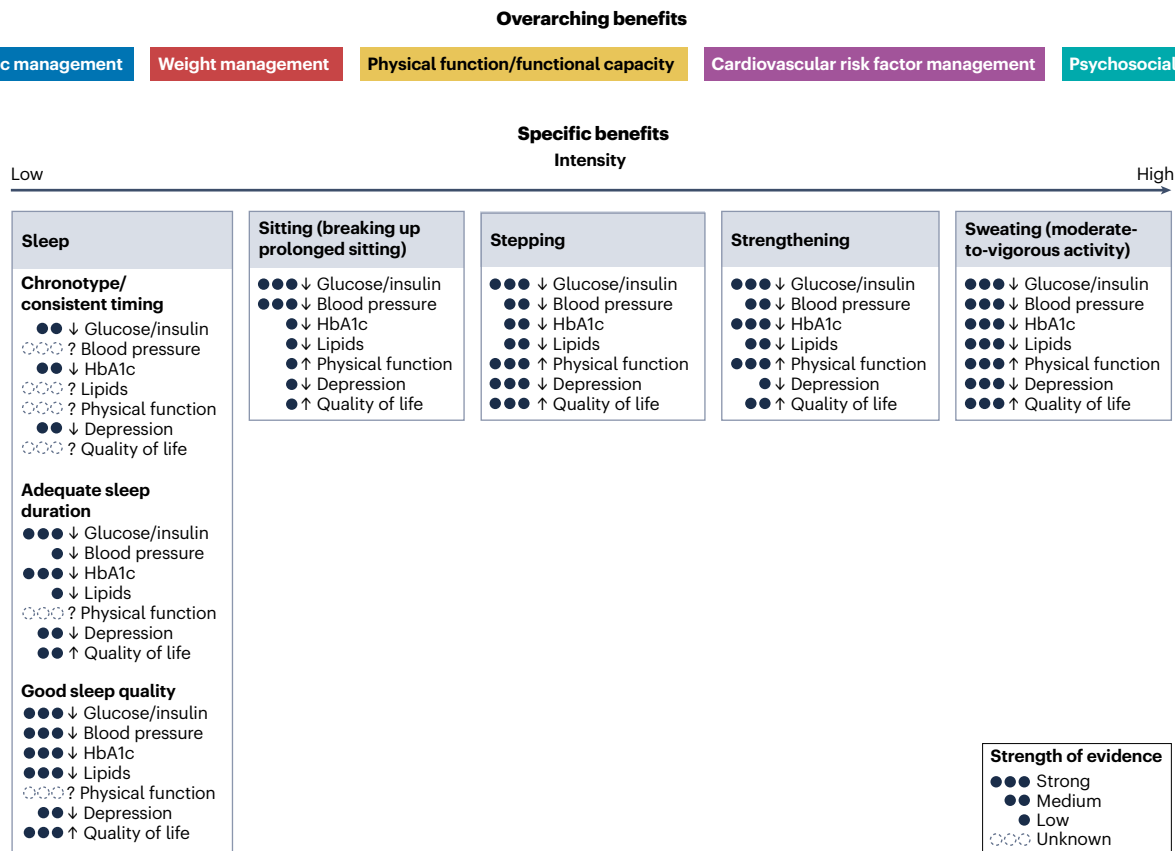


Fig. 7 | The importance of the 24-h physical behaviours for T2DM. All physical behaviours within the 24-h day are associated with clinical outcomes in individuals with type 2 diabetes mellitus (T2DM). These behaviours encompass the five Ss: sitting, stepping, sleep (inclusive of duration, quality and timing),

strengthening and sweating. Outcomes are shown under each heading with a corresponding icon indicating the direction of the association with the exposure (heading) and the number of dots indicates the strength of the evidence.

fading motivation over time as well as behavioural or psychological and environmental or socioeconomic barriers. Long-term success requires continuous support and compliance, structured follow-up and individualized strategies to help sustain change.

Glucose-lowering medications

Nutrient-stimulated hormone-based treatments. Nutrient-stimulated hormone-based therapies harness the body's natural hormonal responses to nutrient intake to improve glycaemic control. These therapies primarily target the incretin system, enhancing the actions of hormones such as GLP1 and GIP, which are released in response to food ingestion. These therapies offer a physiologically targeted and effective approach to managing T2DM and its complications.

GLP1RAs and GLP1RA dual agonists (for example, GLP1-GIP co-agonists) stimulate insulin secretion in a glucose-dependent manner, suppress glucagon release, slow gastric emptying and promote satiety, leading to improved glycaemic control and weight loss²¹. GLP1RAs are a heterogeneous class with multiple agents that vary in their structure, route of administration (oral versus injectable), frequency of administration (daily versus weekly) and their efficacy, which can range from 0.5% to 2.1% reduction in HbA1c and 3% to 14% reduction in body weight (Supplementary Table 1). Two long-acting GLP1RAs

(liraglutide and semaglutide) and the long-acting dual GLP1-GIP receptor agonist tirzepatide are also indicated for chronic weight management and have demonstrated efficacy in this context among people with T2DM; studies have shown weight loss of up to 6.0%²¹³, 10.6%²¹⁴ and 15.6%²¹⁵, respectively.

Some of these agents have demonstrated cardiovascular and renal benefits in addition to their metabolic effects²¹⁶. In a meta-analysis that included all outcome studies for GLP1RAs in people with T2DM, 14% reduction in major adverse cardiovascular outcomes, 12% reduction in all-cause mortality, 14% reduction in hospitalization for heart failure and 17% reduction in composite kidney outcome were noted with these agents²¹⁶. Owing to these demonstrated cardiovascular and kidney benefits, GLP1RAs are considered a foundational treatment for people with T2DM and atherosclerotic cardiovascular disease, with emerging guidelines also supporting their use among those with heart failure (with preserved ejection fraction) and chronic kidney disease.

These agents have been shown to have pleiotropic effects beyond the ones noted above²¹⁷, including substantial improvements in cardiovascular risk factors (for example, triglycerides, free fatty acids, blood pressure, inflammatory markers and waist circumference), improvements in MASH (semaglutide reduced markers of steatohepatitis and fibrosis, leading to specific licensing for use in individuals with

Table 2 | Physical activity and sleep recommendations for adults with T2DM

Component	Recommendation	Frequency/distribution	Key benefits
Aerobic exercise	≥150 min/week moderate intensity or ≥75 min/week vigorous intensity	≥3 days/week; not >2 consecutive days off	Improves insulin sensitivity, glycaemic control, cardiorespiratory fitness
Resistance training	Moderate-to-vigorous intensity	2–3 times/week (non-consecutive days)	Improves glycaemia, strength, balance, functional capacity Counters frailty risk
Sedentary behaviour	Minimize prolonged sitting; break up with light activity	Throughout the day	Confers metabolic benefits
Sleep factor ^a	Definition or association	Association with diabetes outcomes	
Duration (short)	<6h per night	↑ Risk of developing T2DM ↑ Risk of progression in established T2DM	
Duration (optimal)	~7h per night	↓ Risk of T2DM	
Duration (long)	>9h per night	↑ Risk of developing T2DM ↑ Risk of progression in established T2DM	
Sleep quality	Poor quality (for example, fragmentation and insomnia)	↑ T2DM risk and progression	
Chronotype (evening)	Preference for later sleep/wake times	↑ T2DM risk and progression	
Key recommendation	Addressing sleep duration, quality and timing as part of comprehensive diabetes care may help to improve clinical outcomes		

T2DM, type 2 diabetes mellitus. ^aSleep data are predominantly derived from observational studies, and the impact of sleep-based interventions is generally understudied.

MASH²¹⁸), obstructive sleep apnoea and osteoarthritis-associated pain, as well as potential benefits on addictive behaviour (for example, alcohol, gambling and drugs)²¹⁹, all common comorbidities among people with T2DM.

The most common side effects with this class of medications are gastrointestinal in nature and include nausea, vomiting, constipation, diarrhoea, dyspepsia, flatulence, eructation, abdominal pain and abdominal distension. Although these symptoms are commonly mild and self-limited, up to 20% of people discontinue these medications owing to such side effects. Careful education, dose titration and symptom management improve tolerability and drug persistence²²⁰.

Finally, challenges that arise from medication costs may prohibit long-term and equal access to these newer pharmacotherapies^{221,222}. These issues are likely to improve as patents expire and generic forms become available, which is also likely to improve access in regions with limited resources. For example, in many regions, generic forms of dapagliflozin (a sodium–glucose co-transporter 2 (SGLT2) inhibitor) and liraglutide (a GLP1RA) are already available.

DPP4 inhibitors. Dipeptidyl peptidase 4 (DPP4) inhibitors block the DPP4 enzyme, which degrades incretin hormones such as GLP1 and GIP. As such, DPP4 inhibitors are incretin enhancers, prolonging the actions of these hormones and enhancing glucose-dependent insulin secretion and suppression of glucagon release. These agents are weight-neutral, have a low risk of hypoglycaemia and a favourable safety profile, making them suitable for use in older individuals or those at increased risk of hypoglycaemia. However, DPP4 inhibitors have modest glucose-lowering effects (HbA1c lowering of 0.3–0.7%) and do not provide cardiorenal protection.

SGLT2 inhibitors. SGLT2 inhibitors promote glycosuria by inhibiting glucose reabsorption in the proximal renal tubules, leading to improvement in HbA1c of 0.5–1%²²³. The magnitude of glycaemic effect is dependent on baseline glycaemia and kidney function (limited glycaemic effect at estimated glomerular filtration rate (eGFR) levels

<45 ml/min/1.73 m²)²²⁴. Treatment with SGLT2 inhibitors is associated with modest weight loss, usually <5% of the total body weight²²³.

Treatment with several SGLT2 inhibitors in people with T2DM has been shown to improve cardiovascular and kidney outcomes (Supplementary Figs. 2 and 3). Among people with T2DM at high risk for atherosclerotic cardiovascular disease, treatment with SGLT2 inhibitors has shown an average reduction of 9% in the risk of major cardiovascular events²²⁵. Among people with T2DM and heart failure with preserved (or moderately reduced) ejection fraction, SGLT2 inhibitors reduced the risk of a composite of hospitalizations for heart failure and cardiovascular death by -21%²²⁶, whereas among those with heart failure with reduced ejection fraction, the risk reduction was -26%²²⁷. Among people with chronic kidney disease (irrespective of diabetes status), SGLT2 inhibitors have been shown to reduce progression of kidney disease (composite outcome) by 33% but also reduce cardiovascular outcomes, including the risk of major adverse cardiovascular outcomes by 16%, cardiovascular death by 13% and heart failure composite by 33%²²⁸. Owing to these demonstrated cardiovascular and kidney benefits, SGLT2 inhibitors are considered a foundational treatment for people with T2DM and either heart failure, chronic kidney disease or a high risk for atherosclerotic cardiovascular disease, with affordability and accessibility improving considerably as generic forms become available.

The mechanisms of action through which SGLT2 inhibitors exert beneficial cardiovascular and kidney effects are not fully understood; however, they may include plasma volume reduction²²⁹, lipolysis, ketogenesis, enhanced mitochondrial function and ATP efficiency²³⁰, natriuresis²³¹, reduction in myocardial glucotoxicity²³², modulation of iron metabolism²³³, anti-inflammatory actions^{234,235} and reduction in sympathetic tone²³⁶. Although transient eGFR dips are common following initiation of SGLT2 inhibitors, long-term renal preservation is maintained^{237,238}.

Metformin. Since the 1950s, metformin has been a widely used, safe, effective and low-cost treatment option for treating individuals with T2DM. Metformin primarily works by reducing hepatic

glucose production and improving insulin sensitivity in peripheral tissues, thereby lowering blood glucose levels (HbA1c reduction of 0.5–1%) without causing hypoglycaemia. Metformin is weight-neutral, and emerging evidence also suggests that it may reduce the risk of long-term complications^{239,240}, with potential anti-inflammatory benefits. Metformin is typically well tolerated, though gastrointestinal side effects may occur, and its use should be monitored in people with impaired kidney function owing to a small risk of lactic acidosis. Metformin represents a particularly important treatment option in LMICs owing to the low cost of medication, generally increased prevalence of T2DM without obesity and probable organ-protective effects.

Insulin. Despite the availability of numerous oral and non-insulin agents, insulin remains relevant as a therapeutic option owing to the gradual decline in pancreatic β -cell function and mass, which can lead to fasting and postprandial hyperglycaemia^{241,242}. Current guidelines recommend continuing other glucose-lowering agents with insulin initiation, provided there is no evidence of insulin deficiency. GLP1-based therapies (including GLP1–GIP co-agonists) should be used at the maximum tolerated doses before or alongside insulin use, when appropriate^{243,244}.

Basal insulin is typically the first step in initiating insulin therapy. Basal insulin is available in vials or syringes and also in user-friendly

delivery methods such as pens or patch pumps²⁴⁵ (Table 3). Connected pens, smart caps and apps, often integrated with continuous glucose monitoring systems, can assist with dosing through embedded titration algorithms. Although these technologies offer distinct advantages, especially for remote monitoring, they may be challenging for some individuals to use.

Initial basal insulin dosing is usually based on body weight and the degree of hyperglycaemia. Doses should be titrated over days to weeks to achieve and maintain glycaemic goals²⁴³. To minimize the risk of hypoglycaemia owing to excessive basal insulin, prandial (mealtime) insulin must be considered.

Basal insulins can vary in duration of action and cost (Table 4), with costs of specific insulin formulations also varying across regions. First-generation analogues like neutral protamine hagedorn are shorter-acting (~8 h) but are generally more affordable than newly developed insulins. Bedtime neutral protamine hagedorn can help to suppress overnight hepatic glucose production and reduce fasting hyperglycaemia. Next-generation basal insulins, such as degludec and glargine U-300, have durations closer to 24 h, offering more consistent glycaemic control with fewer injections and decreased rates of hypoglycaemia²⁴⁶.

New, once-weekly basal insulins – icodec and efsitora alfa – have completed phase III trials, with icodec already approved in several countries^{247–253}. These insulins offer simplified dosing regimens that

Table 3 | Summary of types of insulin delivery devices for T2DM

Insulin delivery device	Advantages	Disadvantages	Target population	Clinical application
Vial and syringe	Easily available Lower cost	Requires education Less accurate dosing Requires manual dexterity and good vision for dosing	Those with limited access to other forms of insulin delivery	Low-resource settings
Insulin pens	Convenient and user-friendly Accurate dosing Easy for travel	Requires some patient education	Patients needing simple dosing tools Preferable for older people and those with visual or dexterity limitations	Appropriate for those requiring flexible and precise dose adjustments
Connected smart pens and caps	Facilitate integration with apps, continuous glucose monitoring and data transfer Tracks insulin dose timing and temperature Bolus calculator	Connected devices may need frequent troubleshooting App may be overwhelming to manage Variable battery life	People with a desire for algorithm-assisted dosing	May enhance remote patient monitoring
Patch pumps	Tubeless design, lightweight and discreet Greater mobility More affordable than traditional pumps, simple to operate	Frequent device replacement required Potential for catheter occlusion Limited control of basal rates compared with traditional pumps	Patients with T2DM prioritizing convenience and mobility Young adults preferring a modern solution Suitable for those with stable insulin needs	Well suited for people with T2DM needing easy, flexible insulin delivery Used for prandial insulin in social environments to reduce injection-related stigma
Automated insulin devices	More physiological insulin delivery Customizable basal and bolus rates to meet patient needs Minimizes hypoglycaemia	Some are bulky and may restrict movement Frequent interaction is needed, which may increase mental burden or worsen stigma Tubing can kink or disconnect Regular catheter changes needed High cost	People requiring intensive insulin management and frequent dose adjustments	Primarily used for people on multiple-dose injections

T2DM, type 2 diabetes mellitus.

Table 4 | Summary of types of insulin and duration of effect

Insulin type	Examples	Basal or bolus	Onset of action	Duration of action	Comments
Rapid-acting	Lispro, aspart, glulisine, inhaled insulin	Bolus	5–15 min	3–6 h 2–3 h for inhaled insulin	Should be used just before meals or to correct elevated glucose values
Short-acting	Regular	Bolus	30–60 min	5–8 h	Looks clear, administered 30 min before meals
Intermediate-acting daily or twice daily	Neutral protamine hagedorn	Basal	2–4 h	10–16 h	Looks cloudy, should be rolled to mix
Long-acting daily	Glargine	Basal	1–2 h	18–24 h	Should be administered at the same time every day Cannot mix with other insulins
Longer-acting daily	Degludec, glargine U-300	Basal	1–2 h	24–30 h	More flexible delivery Cannot mix with other insulins
Once weekly	Icodec, efsitora	Basal	2–4 h	7–20 days	Consider for convenience and better adherence
Pre-mixed	70/30, 50/50, 75/25	Combined basal and bolus	15–30 min	10–16 h	Beneficial for those needing simplicity to cover meals and overnight hyperglycaemia

can improve adherence and reduce the treatment burden for people with T2DM and caregivers²⁵⁴. Hypoglycaemia rates, as measured by continuous glucose monitoring, remained low across studies, with time below the range <54 mg/dl (3.0 mmol/l) being consistently <1% over trial durations of up to 78 weeks^{250,255–257}. The optimal method of initiation and dose titration remains a topic of debate. Prandial insulin should be added when post-meal glucose levels consistently exceed individual targets. Future insulin formulations include glucose-responsive insulin, which becomes more active at high glucose levels and less active when glucose is low, potentially reducing the risk of hypoglycaemia²⁵⁸.

Insulin secretagogues. Insulin secretagogues, including sulfonylureas and meglitinides, are oral medications that stimulate insulin release from pancreatic β -cells²⁵⁹. They lower blood glucose levels independent of food intake, making them effective in the short term, especially early in the disease course when β -cell function is preserved. However, their use is associated with increased risk of hypoglycaemia and weight gain. Glimpiride and gliclazide are third-generation sulfonylureas with improved efficacy and safety over their predecessors²⁵⁹; these are still used by a large proportion of people with T2DM in LMICs. Although they are low-cost and widely available, insulin secretagogues do not provide cardiovascular or renal benefits and may accelerate β -cell exhaustion over time. As such, their role has diminished with the availability of newer, safer therapies, except where cost is a limiting factor²⁵⁹.

Insulin sensitizers. Thiazolidinediones, such as pioglitazone, improve insulin sensitivity in adipose tissue, liver and muscle, which are core defects in T2DM. Pioglitazone lowers HbA1c by up to 1% and can be particularly useful in people with a high degree of insulin resistance. Pioglitazone has also shown cardiovascular benefits, including a reduction in stroke and myocardial infarction in individuals at high risk, as demonstrated in the PROactive²⁶⁰ and IRIS trials²⁶¹; however, the IRIS trial included individuals with insulin resistance and not T2DM. Additionally, pioglitazone may improve hepatic steatosis and markers of MASLD. Despite its benefits, pioglitazone should be used with caution owing to potential adverse effects such as weight gain, fluid retention

and increased risk of bone fractures and heart failure in susceptible individuals.

Combination therapy. Treatment selection, that is, initiation and intensification, should be guided by the presence of established or high risk of cardiorenal comorbidities, presence of obesity and other obesity-related complications, risk of hypoglycaemia, individual choice, and costs and availability²⁰. Given the relative potency of GLP1-based agents in controlling glucose levels, combinations involving these agents may be particularly effective in managing hyperglycaemia while minimizing risk of complications. Early results suggest additive glycaemic and metabolic benefits through a combination of SGLT2 inhibitors and GLP1-based agents²⁶². As these medications target different aetiological pathways, and both classes of agents reduce risk of microvascular and macrovascular complications, if healthcare resource allows, they should be considered as a first option when combining medications to optimize outcomes²⁶³.

The combination of GLP1-based agents and basal insulin constitutes another combination, which may be particularly useful in individuals with advanced disease and/or β -cell dysfunction. Trial data support the relative safety and efficacy of this combination in lowering glucose levels, although caution is warranted owing to the potential risk of hypoglycaemia²⁶⁴.

Hypoglycaemia and monitoring

Hypoglycaemia – typically defined as low blood glucose levels (that is, <3.9 mmol/l or <70 mg/dl)²⁶⁵ – poses an immediate risk to individuals with diabetes mellitus in those using insulin, sulfonylureas or glinides²⁶⁶. Beyond medication-related risk factors, other risk factors for hypoglycaemia in T2DM include longer duration of T2DM, hypoglycaemia unawareness, chronic kidney disease, alcohol consumption, strenuous exercise, older age, and cognitive impairment and dementia. The cumulative consequences of hypoglycaemia are wide-ranging and span from societal impacts, such as restricted employment and impaired workplace productivity, to reduced awareness of future hypoglycaemia, impaired cognitive function and increased risk of adverse cardiovascular events and mortality^{267,268}. Risk mitigation involves

careful medication management and using the lowest effective doses when high-risk therapies are used.

As symptoms of hypoglycaemia can be unreliable, especially in those with tight glycaemic control or in those unaware of hypoglycaemia, continuous glucose monitoring has become a valuable tool²⁶⁹. Modern continuous glucose monitoring systems offer up to 15 days of wear, real-time alerts and remote data sharing. Guidance on targets for assessment of glycaemic control for most people with T2DM recommends that people spend <4% of time below range (that is, <3.9 mmol/l or <70 mg/dl) and <1% of time below very low range (that is, <3.0 mmol/l or <54 mg/dl)²⁷⁰.

The use of continuous glucose monitoring should be prioritized for populations at high risk, including insulin users. However, challenges remain – sensor accuracy can vary²⁶⁹, especially on the first and last days of wear, devices may detach²⁷¹, and integration with electronic health records is limited²⁷². Aggregators offer some solutions to generate reports, charts and visualizations that highlight trends and patterns in a person's glucose levels and other health indicators that can streamline care. Despite these barriers, continuous glucose monitoring holds promise for hypoglycaemia prevention and behaviour change, particularly if cost and access barriers can be addressed.

Beyond glycaemic management

A considerable proportion of individuals with T2DM experience the additional burden of weight-related comorbidities owing to the interconnected nature of T2DM and obesity. Thus, the optimal management of T2DM increasingly necessitates approaches beyond glycaemic management. Common weight-related comorbidities include cardiovascular disease, chronic kidney disease, MASH–MASLD, obstructive sleep apnoea, osteoarthritis and certain cancers. While best practice guidelines for the management of each comorbidity should be followed in a person with T2DM, comorbidities should also be considered when deciding choice of glucose-lowering therapy (Fig. 8). For some comorbidities, certain glucose-lowering therapies are specifically licensed regardless of diabetes status, which includes the use of SGLT2 inhibitors in individuals with heart failure or chronic kidney disease, and semaglutide is licensed for use in MASH²⁷³. Some therapies may also have additional benefits based on comorbidities despite lacking

a specific licence, for example, both pioglitazone and SGLT2 inhibitors may be beneficial for individuals with MASH^{165,166}. Caution is also warranted for certain therapies, including sulfonylureas and insulin, in individuals with obesity (owing to weight gain) and frailty and/or sarcopenia (owing to the risk of hypoglycaemia).

Given the rising burden of comorbidities in individuals with T2DM, interventions that provide benefit across multiple systems will become ever-more important. Strategies to benefit multiple comorbidities may vary from system-based to individual-level strategies. System-based strategies potentially target models of care that address comorbidities, coordination of care and workforce training, ultimately moving beyond the single-disease approach. Similarly, individual-level interventions that are disease-modifying or that offer multi-system benefits should be prioritized^{274–277}.

Owing, in part, to their effectiveness at inducing considerable weight loss, treatment with GLP1-based medications may offer multi-system benefits, which has already been demonstrated with tirzepatide. Studies have demonstrated improvements with tirzepatide in a range of vascular risk factors, including HbA1c, body weight, triglycerides and low-density lipoprotein cholesterol, and in reducing disease burden and/or symptoms in obstructive sleep apnoea, MASH, osteoarthritis and heart failure^{215,278–282}. Similarly, semaglutide has been shown to reduce cardiovascular disease risk, delay chronic kidney disease progression, reduce complications in heart failure and improve markers of disease in MASH (Supplementary Fig. 4). Lifestyle interventions can also lead to multi-system improvements. Intensive lifestyle intervention in the Look AHEAD trial was compared with diabetes support and education and led to improvements in HbA1c, blood pressure, dyslipidaemia, microvascular complications, obstructive sleep apnoea, geriatric syndrome, incontinence, MASH, multimorbidity, disability and brain structure, and reduced healthcare use and costs. However, lifestyle interventions only showed a reduction in cardiovascular events in a subset of the population who lost >10% of their body weight.

Therapeutic inertia and medication-taking behaviours

Despite evidence that tight glycaemic management leads to better outcomes in T2DM, therapeutic inertia – defined as failure to initiate

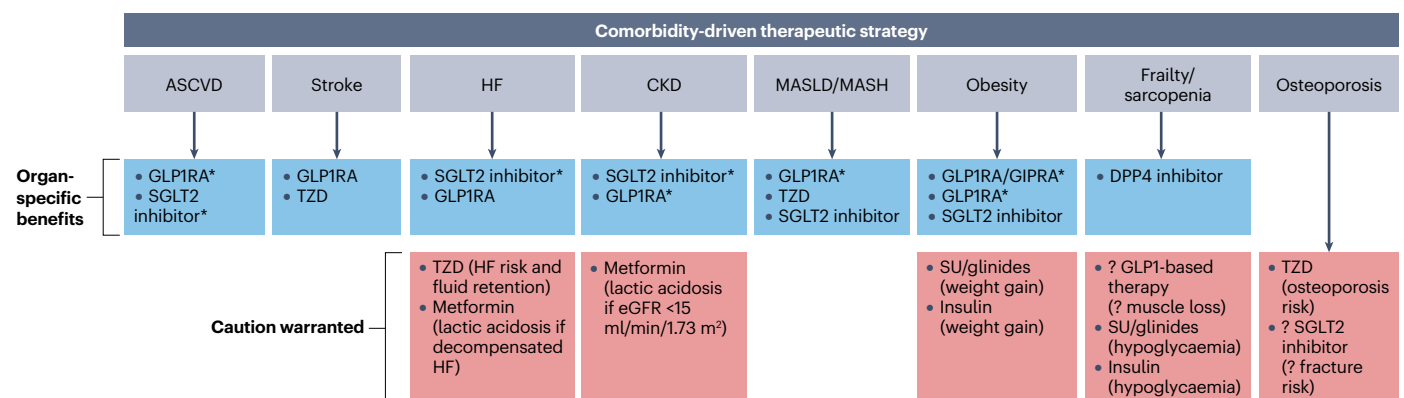


Fig. 8 | Glucose-lowering pharmacotherapy with additional organ-specific benefits for people with T2DM according to their comorbidities.

When choosing appropriate pharmacotherapy for people with type 2 diabetes mellitus (T2DM) and additional comorbidities, agents with organ-specific benefits established with each comorbidity are summarized. Medications for which caution is warranted with certain comorbidities due to potential adverse effects are also highlighted. ASCVD, atherosclerotic cardiovascular

disease; CKD, chronic kidney disease; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; HF, heart failure; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; RA, receptor agonist; SGLT2, sodium/glucose co-transporter 2; SU, sulfonylureas; TZD, thiazolidinediones. *Medications with a specific licence for comorbidity.

or intensify therapy, according to clinical guidelines²⁸³, is a global issue. For example, up to two-thirds of people with T2DM experience therapeutic inertia in the UK²⁸⁴. Individuals with T2DM often experience large delays in receiving indicated medication, with >6 years' delay for intensification with insulin²⁸⁵. The causes of therapeutic inertia are complex and driven by clinician-level, person-level and system-level factors^{286,287}. Therapeutic inertia in a progressive disease such as T2DM can lead to reduced likelihood of achieving target levels later in the disease trajectory²⁸⁸, ultimately increasing complications and mortality. Therapeutic inertia potentially accounts for 80% of cardiovascular events^{285,287}. Methods for overcoming therapeutic inertia can also be addressed by provider-level, person-level and system-level approaches²⁸⁷.

The effectiveness of pharmacological interventions in T2DM management is dependent upon medication-taking behaviours and persistence with therapy plans (that is, continued medication use). Suboptimal medication-taking behaviour has been shown to affect almost 50% of people with T2DM and contributes to increased risks of complications and mortality as well as increased healthcare costs^{289,290}. A range of factors contribute to poorer medication-taking behaviours and early treatment discontinuation in people with T2DM, including concerns about medication effectiveness, fear of hypoglycaemia, limited access to medications and unwanted adverse effects²⁹¹. Addressing key facilitators, such as strong social, family and healthcare provider support, motivation, education and reliable access can help improve medication-taking behaviours²⁹².

Quality of life

Quality of life is often impaired in people with T2DM; therefore, optimizing quality of life is a key target of the principles of person-centred care in T2DM²⁰. Impaired quality of life can be related to the physical and psychological effects of diabetes complications, the burden of multiple long-term conditions, the psychological burden of T2DM and stigma.

Approximately one in four adults with T2DM experiences comorbid depression¹¹⁴, although prevalence varies considerably between geographical regions and assessment methods used¹²⁹³. Diabetes distress encompasses a range of negative emotions associated with living with the condition such as feeling overwhelmed by the demands of self-management¹¹⁵. Diabetes distress is experienced by approximately one-third of people living with T2DM¹¹⁵. Both depression and diabetes distress are associated with impaired diabetes-related outcomes, culminating in poor disease self-management and worse health outcomes²⁹⁴. Notably, early identification and appropriate treatment, whether through psychotherapy, group therapy, lifestyle interventions or medication, is essential to alleviating the rising burden of depression and distress in people with T2DM.

Diabetes stigma, defined as negative social judgements, stereotypes and prejudices about diabetes or about a person or group because they have diabetes, affects ~80% of individuals living with T2DM. Diabetes stigma is driven primarily by blame, perceptions of burden or sickness, invisibility, and fear or disgust and can include assumptions that individuals are sick, weak, lazy or lacking motivation, willpower, self-control or capability, or that they are to blame for their condition and/or health outcomes. Diabetes stigma occurs across a wide range of settings and is pervasive throughout society across multiple countries and cultures. Healthcare professionals may contribute to diabetes stigma, for example, by blaming, judging and/or mistrusting people with diabetes. Diabetes stigma is associated with poorer health outcomes, physical well-being and self-care, psychological well-being, quality of

life and social well-being, as well as with ill effects of discrimination experienced at work, in education or other areas in society²⁹⁵.

Efforts to end diabetes stigma are imperative, which will require action from all sectors of the community, including from within research, healthcare, industry, policy and media, and must involve individuals with lived experience²⁹⁶. The Language Matters movement is a notable example of steps towards ending diabetes stigma, started by Diabetes Australia, and soon followed by other advocacy groups across the world²⁹⁷.

Outlook

Underserved populations

Decisions regarding the treatment of specific populations with T2DM may be limited by their under-representation within clinical trials. Such populations include older adults, women, various minority ethnic groups and adults with EOT2D. In some populations, this under-representation may be compounded by disproportionately high rates of diabetes complications and adverse outcomes²⁹⁸. Strikingly, >80% of people with diabetes worldwide reside in LMICs, with >50% of these people remaining undiagnosed^{29,299}. This disparity represents an important global healthcare burden, underlined by contributing factors such as resource constraints that preclude routine screening and access to simple diagnostic tools, lack of awareness and education among healthcare professionals and people at risk of T2DM, and the largely asymptomatic nature of T2DM early in the disease course. As a result, diabetes research has remained predominantly within the context of higher-income countries, meaning that clinical guidelines are often inadequate in LMICs³⁰⁰.

Early-onset T2DM

The under-representation of people with EOT2D within research is of particular concern³⁰¹. The incidence of EOT2D is rapidly increasing, driven predominantly by the rising prevalence of overweight and obesity in younger individuals, disproportionately affecting people from ethnic minority groups^{302,303} and people with higher socioeconomic deprivation³⁰⁴. EOT2D is underpinned by a high-risk phenotype, characterized by increased BMI, lower physical activity levels, and a higher prevalence of dyslipidaemia than in individuals diagnosed with T2DM later in life⁵. This extreme risk factor profile in people with EOT2D results in a higher risk of complications^{305,306} and a shorter life expectancy⁴⁵. EOT2D is also associated with a greater burden of mental illness, such as anxiety, depression and diabetes-related distress^{10,307}, which may impair quality of life and contribute to low engagement with traditional models of healthcare. This transition to EOT2D poses a considerable societal and healthcare burden worldwide³⁰, necessitating future management approaches that are tailored to the unique metabolic and psychosocial factors in this population³⁰⁸.

Models of care

Integrated chronic care models offer opportunities for improved care outcomes³⁰⁹ given the chronicity of T2DM, despite uncertainty of effect in LMICs. Models of care simplify the process of navigating the complex interplay between diabetes progression and sociocultural and economic circumstances, and impact positively on long-term diabetes outcomes.

The Chronic Care Model of Wagner et al. posits that a prepared practice team interacting with an activated person results in improved outcomes³¹⁰. The components of this model are self-management

education, healthcare financing, service delivery, decision support, health information systems and community linkages. Ideally, institutions should be deliberate about optimizing each of these components when delivering care to people with diabetes mellitus. However, implementing the chronic care model in resource-constrained settings, where insurance coverage is minimal and where people must pay out-of-pocket, is challenging.

Precision medicine and therapeutic options

An unprecedented increase in the number of medications licensed for T2DM and obesity is expected to happen within the next decade^{21,22}. Following the successes of tirzepatide, other medications with actions on multiple enteropancreatic hormones will become commonplace (Supplementary Tables 2, 3 and 4). For example, several GLP1–glucagon co-agonists (mazdutide and survodutide), a GLP1–GIP–glucagon triple agonist (retatrutide), a combination of GLP1 and amylin agonists (CagriSema), and a GLP agonist and GIP antagonist (MariTide) are in late stages of development¹⁹. Phase II data suggest that all of these agents lead to improvements in weight and glucose levels in individuals with T2DM^{273,311–314}.

The increase in available therapeutic options will have the potential to enable greater personalization of care, with certain agents potentially being more effective in certain populations. For example, medications with glucagon-receptor agonism may be particularly effective in reducing hepatic steatosis for individuals with MASH–MASLD owing to direct actions in the liver in addition to their weight-lowering effects^{315–317}. Similarly, medications with non-enteropancreatic targets may offer additional benefits, such as preservation of lean mass with weight loss, with agents such as bimagrumab, an activin type II receptor inhibitor³¹⁸, or addition of a selective androgen receptor modulator such as enobosarm to a GLP1-based medication, which may be most relevant to populations at risk of frailty.

In addition to T2DM management, newer medications may also be effective at preventing or delaying the onset of T2DM. For example, in people with obesity and prediabetes, semaglutide resulted in superior rates of reversion to normoglycaemia³¹⁹ and treatment with tirzepatide was associated with -94% reduction in progression to T2DM compared with placebo³²⁰.

A better understanding of the heterogeneity of T2DM presentation and progression utilizing newer techniques, such as genetic sequencing, machine learning and omics approaches, would improve identification of atypical T2DM and further refine precision medicine interventions^{321,322}. Regarding medication, as well as crude personalization based on comorbidities or functional status, advances in genetics and artificial intelligence may allow greater prediction of treatment response across multiple agents and multiple actions. Indeed, combining mono-receptor agonists, rather than uni-molecular polyagonists, could lead to even greater flexibility and optimization of the ideal ratio of receptor agonism or antagonism for an individual. As well as CagriSema, trials are under way investigating the combination of tirzepatide with various other medications, including eloralintide³²³ (NCT06603571), an amylin receptor agonist; mibavademab³²⁴, a leptin receptor agonist (NCT06373146); bremelanotide³²⁵, a melanocortin 4 receptor agonist (NCT06565611); and bioglutide³²⁶, an oral IGF1–GLP1–GIP–glucagon quadruple agonist (NCT06564753).

Use of technology

Innovations in technological approaches to diabetes care offer great promise in an increasingly digital world. Technology may be applied to

each element of the chronic care model to enhance access and quality of care³²⁷.

At the health system level, IT systems and electronic medical records allow for the creation of registries to aid in identifying people at high risk or those not meeting treatment goals. Furthermore, financially incentivizing healthcare providers to not only deliver high-quality clinical care but also to report data further bolsters the power of electronic medical records, evidenced in the Quality and Outcomes Framework in England³²⁸.

Examples of community-level approaches include digital means of delivering healthcare such as telemedicine (eHealth) and mobile health (mHealth). These approaches involve various elements, such as video conferencing, remote monitoring and SMS and/or website-based interventions, enabling efficient remote data sharing and clinical decision-making while potentially enhancing engagement and satisfaction. Systematic reviews corroborate the potential for glycaemic improvement via telemedicine, although heterogeneity exists, influenced by individual education, attitude and cost^{195,329}. This digital convergence addresses equity gaps, considerably improving access for rural populations and ethnic minorities through culturally tailored interfaces³³⁰.

The utility of digital technologies in supporting diabetes self-management is evidenced in the expanding landscape of device technologies, including continuous glucose monitoring sensors, insulin pumps and closed-loop insulin therapy, all of which have been recommended internationally for people with T1DM¹⁴⁸. More meta-analyses solidify the efficacy of continuous glucose monitoring sensors across the T2DM spectrum, even in non-insulin-treated individuals. Notable HbA1c reductions (-0.32%, 95% CI -0.46 to -0.18) and improved time in range (+8.7%, 95% CI 5.2–12.2) have been demonstrated without increased hypoglycaemia risk in this population³³¹. Critically, time in range improvements – recognized as a superior predictor of microvascular outcomes than HbA1c alone²⁷⁰ – are consistently achieved with continuous glucose monitoring in T2DM. Furthermore, the reduction in hypoglycaemia risk holds particular importance for vulnerable populations such as older individuals. Real-world registry data corroborate sustained benefits, revealing HbA1c reductions (-0.52%) maintained over 24 months regardless of therapeutic regimen³³².

The personalization potential is further amplified by machine learning. Machine learning algorithms analyse vast datasets (electronic health records, demographics, historical responses, real-time continuous glucose monitoring or lifestyle data) to inform optimized treatment decisions³³³. This approach enables more proactive management with real-time adjustments and fosters a collaborative environment essential for optimal care.

Despite compelling evidence, implementation barriers hinder widespread adoption, while digital literacy gaps necessitate user-centred design and adaptive interfaces. Promising solutions include a secure decentralized database for enhanced data security. However, urgent policy priorities remain, particularly reimbursement parity for digital tools and establishing standardized frameworks for validating machine learning algorithms in clinical practice.

Finally, clinical decision aids and support software can facilitate shared decision-making and person-centred care by offering people with T2DM evidence-based information regarding various lifestyle and medication-based management options, helping to educate them to choose their own preferred treatment path³³⁴. Integrating tools and resources to address social determinants of health into clinical guidelines, decision aids and electronic health systems represents a

crucial step towards improving diabetes outcomes and reducing care disparities. Notably, cost and poor health and digital literacy can be barriers to diabetes technology in LMICs and high-income countries, making equity of access across all nations and socioeconomic groups a key challenge³³⁵.

Published online: 19 March 2026

References

1. Lascar, N. et al. Type 2 diabetes in adolescents and young adults. *Lancet Diabetes Endocrinol.* **6**, 69–80 (2018).
This review examines the epidemiology, pathophysiology and clinical challenges of T2DM in adolescents and young adults.
2. *IDF Diabetes Atlas 2025* <https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/> (International Diabetes Federation, 2025).
3. Goldney, J. et al. Burden of vascular risk factors by age, sex, ethnicity and deprivation in young adults with and without newly diagnosed type 2 diabetes. *Diabetes Res. Clin. Pract.* **220**, 112002 (2025).
4. Barker, M. M. et al. Age at type 2 diabetes diagnosis and cause-specific mortality: observational study of primary care patients in England. *Diabetes Care* **46**, 1965–1972 (2023).
5. Barker, M. M. et al. Age at diagnosis of type 2 diabetes and cardiovascular risk factor profile: a pooled analysis. *World J. Diabetes* **13**, 260–271 (2022).
6. Petrak, F., Baumeister, H., Skinner, T. C., Brown, A. & Holt, R. I. G. Depression and diabetes: treatment and health-care delivery. *Lancet Diabetes Endocrinol.* **3**, 472–485 (2015).
7. Srikanth, V., Sinclair, A. J., Hill-Briggs, F., Moran, C. & Biessels, G. J. Type 2 diabetes and cognitive dysfunction-towards effective management of both comorbidities. *Lancet Diabetes Endocrinol.* **8**, 535–545 (2020).
8. Harding, J. L., Pavkov, M. E., Magliano, D. J., Shaw, J. E. & Gregg, E. W. Global trends in diabetes complications: a review of current evidence. *Diabetologia* **62**, 3–16 (2019).
9. Gregg, E. W. et al. Multiple long-term conditions as the next transition in the global diabetes epidemic. *Commun. Med.* **5**, 42 (2025).
10. Gregg, E. W. et al. The burden of diabetes-associated multiple long-term conditions on years of life spent and lost. *Nat. Med.* **30**, 2830–2837 (2024).
11. Multiple long-term conditions (multimorbidity): a priority for global health research. *The Academy of Medical Sciences* <https://acmedsci.ac.uk/policy/policy-projects/multimorbidity> (2026).
12. Khunti, K. et al. Diabetes and multiple long-term conditions: a review of our current global health challenge. *Diabetes Care* **46**, 2092–2101 (2023).
13. Coles, B. et al. Rates and estimated cost of primary care consultations in people diagnosed with type 2 diabetes and comorbidities: a retrospective analysis of 8.9 million consultations. *Diabetes Obes. Metab.* **23**, 1301–1310 (2021).
14. Sancho-Mestre, C. et al. Pharmaceutical cost and multimorbidity with type 2 diabetes mellitus using electronic health record data. *BMC Health Serv. Res.* **16**, 394 (2016).
15. Ling, S. et al. Association of type 2 diabetes with cancer: a meta-analysis with bias analysis for unmeasured confounding in 151 cohorts comprising 32 million people. *Diabetes Care* **43**, 2313–2322 (2020).
16. Lingvay, I., Sumithran, P., Cohen, R. V. & Le Roux, C. W. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* **399**, 394–405 (2022).
17. Anjana, R. M. et al. Contrasting associations between diabetes and cardiovascular mortality rates in low-, middle-, and high-income countries: cohort study data from 143,567 individuals in 21 countries in the PURE study. *Diabetes Care* **43**, 3094–3101 (2020).
18. Shivashankar, R. et al. Quality of diabetes care in low- and middle-income Asian and Middle Eastern countries (1993–2012): 20-year systematic review. *Diabetes Res. Clin. Pract.* **107**, 203–223 (2015).
19. Agardh, E., Allebeck, P., Hallqvist, J., Moradi, T. & Sidorchuk, A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. *Int. J. Epidemiol.* **40**, 804–818 (2011).
20. Davies, M. J. et al. Management of hyperglycemia in type 2 diabetes, 2022. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **45**, 2753–2786 (2022).
This consensus provides updated global recommendations for management of hyperglycaemia in T2DM from the American Diabetes Association and the European Association for the Study of Diabetes.
21. Melson, E., Ashraf, U., Papamargaritis, D. & Davies, M. J. What is the pipeline for future medications for obesity? *Int. J. Obes.* **49**, 433–451 (2025).
This review summarizes the therapeutic pipeline for future obesity treatments.
22. Goldney, J. & Davies, M. J. GLP1 agonists: current and future landscape of clinical trials for patients with metabolic dysfunction. *Nat. Rev. Gastroenterol. Hepatol.* **21**, 664–666 (2024).
This review outlines the current and future clinical trial landscape for GLP1RAs.
23. American Diabetes Association Professional Practice Committee. 13. Older adults: standards of care in diabetes — 2025. *Diabetes Care* **48**, S266–S282 (2024).
24. Laiteerapong, N. & Huang, E. S. In *Diabetes in America* (eds Cowie, C. C. et al.) Ch. 16 (National Institute of Diabetes and Digestive and Kidney Diseases, 2018).
25. *National Diabetes Statistics Report* <https://www.cdc.gov/diabetes/php/data-research/index.html> (US Centers for Disease Control and Prevention, 2024).
26. Golden, S. H., Yajnik, C., Phatak, S., Hanson, R. L. & Knowler, W. C. Racial/ethnic differences in the burden of type 2 diabetes over the life course: a focus on the USA and India. *Diabetologia* **62**, 1751–1760 (2019).
27. Phelps, N. H. et al. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet* **403**, 1027–1050 (2024).
28. Jaacks, L. M. et al. The obesity transition: stages of the global epidemic. *Lancet Diabetes Endocrinol.* **7**, 231–240 (2019).
29. Zhou, B. et al. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet* **404**, 2077–2093 (2024).
This study provides a global pooled analysis of 141 million participants, showing long-term trends in diabetes prevalence and treatment.
30. Luk, A. et al. Early-onset type 2 diabetes: the next major diabetes transition. *Lancet* **405**, 2313–2326 (2025).
31. Butler, A. M. & Eddington, A. Disparities in youth-onset type 2 diabetes. *Endocrinol. Metab. Clin. N. Am.* **54**, 225–232 (2025).
32. Perrig, W., Conway, R., Mayer-Davis, E. & Dabelea, D. Youth-onset type 2 diabetes: the epidemiology of an awakening epidemic. *Diabetes Care* **46**, 490–499 (2023).
33. Narayan, K. M. V. et al. Copenhagen Declaration: a transformative vision for global diabetes. *Lancet Diabetes Endocrinol.* **13**, 543–545 (2025).
This report sets out the Copenhagen Declaration, a global vision for transformative diabetes prevention and care.
34. Beyh, Y. S. et al. *Copenhagen Declaration: A Blueprint for Diabetes Care and Research in an Inter-connected World* <http://diabetes.emory.edu/copenhagen-diabetes-declaration/index.html> (Global Diabetes Forum, 2024).
35. Hill-Briggs, F. et al. Social determinants of health and diabetes: a scientific review. *Diabetes Care* **44**, 258–279 (2020).
36. den Braver, N. R. et al. Built environmental characteristics and diabetes: a systematic review and meta-analysis. *BMC Med.* **16**, 12 (2018).
37. Chan, J. C. N. et al. The lancet commission on diabetes: using data to transform diabetes care and patient lives. *Lancet* **396**, 2019–2082 (2020).
38. O’Hearn, M. et al. Incident type 2 diabetes attributable to suboptimal diet in 184 countries. *Nat. Med.* **29**, 982–995 (2023).
39. Goff, L. M. Ethnicity and type 2 diabetes in the UK. *Diabet. Med.* **36**, 927–938 (2019).
40. Diabetes. *World Health Organization* <https://www.who.int/news-room/fact-sheets/detail/diabetes> (2024).
41. Institute for Health Metrics and Evaluation. *Global Burden of Disease Study 2019. Global Health Data Exchange* <https://vizhub.healthdata.org/gbd-results> (2020).
42. Balooch Hasankhani, M., Mirzaei, H. & Karamoozian, A. Global trend analysis of diabetes mellitus incidence, mortality, and mortality-to-incidence ratio from 1990 to 2019. *Sci. Rep.* **13**, 21908 (2023).
43. Rawshani, A. et al. Association between socioeconomic status and mortality, cardiovascular disease, and cancer in patients with type 2 diabetes. *JAMA Intern. Med.* **176**, 1146–1154 (2016).
44. Gregg, E. W. et al. Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985–2011: a model study. *Lancet Diabetes Endocrinol.* **2**, 867–874 (2014).
45. Kaptoge, S. et al. Life expectancy associated with different ages at diagnosis of type 2 diabetes in high-income countries: 23 million person-years of observation. *Lancet Diabetes Endocrinol.* **11**, 731–742 (2023).
46. Chen, L. et al. A systematic review of trends in all-cause mortality among people with diabetes. *Diabetologia* **63**, 1718–1735 (2020).
47. Gregg, E. W. et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. *Lancet* **391**, 2430–2440 (2018).
48. Holman, N. et al. Trends in mortality and hospitalisations for cardiovascular, kidney and liver disease in people with type 2 diabetes in England, 2009–2019. *Diabetes Obes. Metab.* **27**, 6341–6352 (2025).
49. Huang, G. et al. Decomposing the differences in healthy life expectancy between migrants and natives: the ‘healthy migrant effect’ and its age variations in Australia. *J. Pop. Res.* **41**, 3 (2023).
50. Anand, S. S. et al. Reducing inequalities in cardiovascular disease: focus on marginalized populations considering ethnicity and race. *Lancet Reg. Health Eur.* **56**, 101371 (2025).
51. Harding, J. L. et al. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997–2010. *Diabetes Care* **37**, 2579–2586 (2014).
52. Pearson-Stuttard, J. et al. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. *Lancet Diabetes Endocrinol.* **9**, 165–173 (2021).
53. Bjornsdottir, H. H. et al. A national observation study of cancer incidence and mortality risks in type 2 diabetes compared to the background population over time. *Sci. Rep.* **10**, 17376 (2020).
54. European Association for the Study of Obesity. *Study of UK biobank reveals link between new-onset type 2 diabetes and some but not all obesity-related cancers. EurekAlert!* <https://www.eurekalert.org/news-releases/1077674> (22 March 2025).

55. Renehan, A. G., Tipping, O. & Wang, M. Diabetes and cancer: doubts of a causal link. *Int. J. Cancer* **154**, 1875–1876 (2024).
56. Zaccardi, F. et al. Trajectories of type 2 diabetes and cancer in 330 000 individuals with prediabetes: 20-year observational study in England. *Lancet Diabetes Endocrinol.* **14**, 41–49 (2026).
57. Zhang, A. M. Y., Wellberg, E. A., Kopp, J. L. & Johnson, J. D. Hyperinsulinemia in obesity, inflammation, and cancer. *Diabetes Metab. J.* **45**, 285–311 (2021).
58. Lincoff, A. M. et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N. Engl. J. Med.* **389**, 2221–2232 (2023).
59. Butler, A. E. et al. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* **52**, 102–110 (2003).
60. Moon, J. H., Choe, H. J. & Lim, S. Pancreatic beta-cell mass and function and therapeutic implications of using antidiabetic medications in type 2 diabetes. *J. Diabetes Investig.* **15**, 669–683 (2024).
61. Ahmad, E., Lim, S., Lamptey, R., Webb, D. R. & Davies, M. J. Type 2 diabetes. *Lancet* **400**, 1803–1820 (2022).
62. Hanley, S. Pancreatic β -cell mass as a pharmacologic target in diabetes. *McGill J. Med.* **12**, 51 (2009).
63. Donath, M. Y. & Halban, P. A. Decreased beta-cell mass in diabetes: significance, mechanisms and therapeutic implications. *Diabetologia* **47**, 581–589 (2004).
64. Fiaschi-Taesch, N. M. et al. Induction of human beta-cell proliferation and engraftment using a single G1/S regulatory molecule, CDK6. *Diabetes* **59**, 1926–1936 (2010).
65. Acefifi, C. et al. GLP-1 receptor agonists synergize with DYRK1A inhibitors to potentiate functional human β cell regeneration. *Sci. Transl. Med.* **12**, eaaw9996 (2020).
66. Wang, P. et al. A high-throughput chemical screen reveals that harmine-mediated inhibition of DYRK1A increases human pancreatic beta cell replication. *Nat. Med.* **21**, 383–388 (2015).
67. Wang, P. et al. Combined Inhibition of DYRK1A, SMAD, and trithorax pathways synergizes to induce robust replication in adult human beta cells. *Cell Metab.* **29**, 638–652.e5 (2019).
68. Talchai, C., Xuan, S., Lin, H. V., Sussel, L. & Accili, D. Pancreatic β cell dedifferentiation as a mechanism of diabetic β cell failure. *Cell* **150**, 1223–1234 (2012).
69. Zhou, Y. et al. METRNL represses beta-to-alpha cell trans-differentiation to maintain beta cell function under diabetic metabolic stress in mice. *Diabetologia* **68**, 1769–1788 (2025).
70. Nguyen, H. T. et al. Palmitate impairs autophagic degradation via oxidative stress/perilysosomal Ca^{2+} overload/mTORC1 activation pathway in pancreatic β cells. *JCI Insight* **10**, e192827 (2025).
71. Alanazi, Y. A. et al. Role of autophagy in type 2 diabetes mellitus: the metabolic clash. *J. Cell Mol. Med.* **28**, e70240 (2024).
72. Uchida, M. et al. Multiorgan fibrosis and risk of type 2 diabetes: genetic and observational evidence highlighting a causal role of pancreatic fibrosis. *Diabetes* <https://doi.org/10.2337/db25-0629> (2026).
73. Cheng, C.-W. et al. Fasting-mimicking diet promotes ngn3-driven β -cell regeneration to reverse. *Diabetes Cell* **168**, 775–788.e12 (2017).
74. Taylor, R. Calorie restriction and reversal of type 2 diabetes. *Expert Rev. Endocrinol. Metab.* **11**, 521–528 (2016).
75. Accili, D., Deng, Z. & Liu, Q. Insulin resistance in type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **21**, 413–426 (2025).
- This review synthesizes current understanding of insulin resistance mechanisms in T2DM.**
76. Roden, M. & Shulman, G. I. The integrative biology of type 2 diabetes. *Nature* **576**, 51–60 (2019).
77. Rabiee, A., Hossain, M. A. & Poojari, A. Adipose tissue insulin resistance: a key driver of metabolic syndrome pathogenesis. *Biomedicines* **13**, 2376 (2025).
78. Saltiel, A. R. & Olefsky, J. M. Inflammatory mechanisms linking obesity and metabolic disease. *J. Clin. Invest.* **127**, 1–4 (2017).
79. Neeland, I. J. et al. Metabolic syndrome. *Nat. Rev. Dis. Primers* **10**, 77 (2024).
80. Chavakis, T., Alexaki, V. I. & Ferrante, A. W. Macrophage function in adipose tissue homeostasis and metabolic inflammation. *Nat. Immunol.* **24**, 757–766 (2023).
81. Tchernof, A. & Després, J.-P. Pathophysiology of human visceral obesity: an update. *Physiol. Rev.* **93**, 359–404 (2013).
82. Sylow, L., Tokarz, V. L., Richter, E. A. & Klip, A. The many actions of insulin in skeletal muscle, the paramount tissue determining glycemia. *Cell Metab.* **33**, 758–780 (2021).
83. Kim, H.-K. et al. Association of visceral fat obesity, sarcopenia, and myosteatosis with non-alcoholic fatty liver disease without obesity. *Clin. Mol. Hepatol.* **29**, 987–1001 (2023).
84. Callahan, H. S. et al. Postprandial suppression of plasma ghrelin level is proportional to ingested caloric load but does not predict intermeal interval in humans. *J. Clin. Endocrinol. Metab.* **89**, 1319–1324 (2004).
85. Huang, Y. et al. Low thigh muscle strength in relation to myosteatosis in patients with type 2 diabetes mellitus. *Sci. Rep.* **13**, 1957 (2023).
86. Lu, X. et al. Thigh muscle fat fraction is independently associated with impaired glucose metabolism in individuals with obesity. *Endocr. Connect.* **12**, e230248 (2023).
87. Choe, H. J., Chang, W., Blüher, M., Heymsfield, S. B. & Lim, S. Independent association of thigh muscle fat density with vascular events in Korean adults. *Cardiovasc. Diabetol.* **23**, 44 (2024).
88. Savage, D. B. et al. Accumulation of saturated intramyocellular lipid is associated with insulin resistance. *J. Lipid Res.* **60**, 1323–1332 (2019).
89. Szendroedi, J. et al. Role of diacylglycerol activation of PKC θ in lipid-induced muscle insulin resistance in humans. *Proc. Natl Acad. Sci. USA* **111**, 9597–9602 (2014).
90. Goodpaster, B. H., Kelley, D. E., Wing, R. R., Meier, A. & Thaete, F. L. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes* **48**, 839–847 (1999).
91. Manini, T. M. et al. Reduced physical activity increases intermuscular adipose tissue in healthy young adults. *Am. J. Clin. Nutr.* **85**, 377–384 (2007).
92. Mehta, M., Shah, J. & Joshi, U. Understanding insulin resistance in NAFLD: a systematic review and meta-analysis focused on HOMA-IR in South Asians. *Cureus* **16**, e70768 (2024).
93. Shulman, G. I. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N. Engl. J. Med.* **371**, 1131–1141 (2014).
94. James, D. E., Stöckli, J. & Birnbaum, M. J. The aetiology and molecular landscape of insulin resistance. *Nat. Rev. Mol. Cell Biol.* **22**, 751–771 (2021).
95. Samuel, V. T. & Shulman, G. I. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. *J. Clin. Invest.* **126**, 12–22 (2016).
96. Koliaki, C. & Roden, M. Alterations of mitochondrial function and insulin sensitivity in human obesity and diabetes mellitus. *Annu. Rev. Nutr.* **36**, 337–367 (2016).
97. Xourafa, G., Korbacher, M. & Roden, M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **20**, 27–49 (2024).
98. Kubota, N. et al. Differential hepatic distribution of insulin receptor substrates causes selective insulin resistance in diabetes and obesity. *Nat. Commun.* **7**, 12977 (2016).
99. Lim, S., Taskinen, M.-R. & Borén, J. Crosstalk between nonalcoholic fatty liver disease and cardiometabolic syndrome. *Obes. Rev.* **20**, 599–611 (2019).
100. Rinella, M. E. et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* **78**, 1966–1986 (2023).
101. Younossi, Z. M. et al. Global consensus recommendations for metabolic dysfunction-associated steatotic liver disease and steatohepatitis. *Gastroenterology* **169**, 1017–1032.e2 (2025).
102. Huang, D. Q. et al. Metabolic dysfunction-associated steatotic liver disease in adults. *Nat. Rev. Dis. Primers* **11**, 14 (2025).
103. Holst, J. J., Vilsbøll, T. & Deacon, C. F. The incretin system and its role in type 2 diabetes mellitus. *Mol. Cell. Endocrinol.* **297**, 127–136 (2009).
104. Mlynarska, E. et al. Exploring the significance of gut microbiota in diabetes pathogenesis and management — a narrative review. *Nutrients* **16**, 1938 (2024).
105. Mueller, N. T. et al. Metformin affects gut microbiome composition and function and circulating short-chain fatty acids: a randomized trial. *Diabetes Care* **44**, 1462–1471 (2021).
106. Lassenius, M. I. et al. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. *Diabetes Care* **34**, 1809–1815 (2011).
107. Liu, S., Tao, Z., Qiao, M. & Shi, L. The functions of major gut microbiota in obesity and type 2 diabetes. *Metabolites* **15**, 167 (2025).
108. DeFronzo, R. A. et al. Inadequately controlled type 2 diabetes and hypercortisolism: improved glycemia with mifepristone treatment. *Diabetes Care* <https://doi.org/10.2337/dc25-1055> (2025).
109. Buse, J. B. et al. Prevalence of hypercortisolism in difficult-to-control type 2 diabetes. *Diabetes Care* <https://doi.org/10.2337/dc24-2841> (2025).
110. Suzuki, K. et al. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature* **627**, 347–357 (2024).
- This study defines genetic drivers of heterogeneity in T2DM pathophysiology using large-scale genomic analyses.**
111. Bonnefond, A., Florez, J. C., Loos, R. J. F. & Froguel, P. Dissection of type 2 diabetes: a genetic perspective. *Lancet Diabetes Endocrinol.* **13**, 149–164 (2025).
112. Bonnefond, A. et al. Monogenic diabetes. *Nat. Rev. Dis. Primers* **9**, 12 (2023).
113. Hinault, C., Caroli-Bosc, P., Bost, F. & Chevalier, N. Critical overview on endocrine disruptors in diabetes mellitus. *Int. J. Mol. Sci.* **24**, 4537 (2023).
114. Khaledi, M., Haghghatdoost, F., Feizi, A. & Aminorroaya, A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetol.* **56**, 631–650 (2019).
- This meta-analysis shows a high prevalence of comorbid depression in people with T2DM.**
115. Perrin, N. E., Davies, M. J., Robertson, N., Snoek, F. J. & Khunti, K. The prevalence of diabetes-specific emotional distress in people with type 2 diabetes: a systematic review and meta-analysis. *Diabet. Med.* **34**, 1508–1520 (2017).
116. Brownlee, M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* **54**, 1615–1625 (2005).
117. Madonna, R., Balistreri, C. R., Geng, Y.-J. & De Caterina, R. Diabetic microangiopathy: pathogenetic insights and novel therapeutic approaches. *Vasc. Pharmacol.* **90**, 1–7 (2017).
118. Pushparani, D. S., Varalakshmi, J., Roobini, K., Hamshapriya, P. & Livitha, A. Diabetic retinopathy — a review. *Curr. Diabetes Rev.* **21**, 43–55 (2025).
119. Tang, S. C. W. & Yiu, W. H. Innate immunity in diabetic kidney disease. *Nat. Rev. Nephrol.* **16**, 206–222 (2020).
120. Aziz, N. et al. New horizons in diabetic neuropathies: an updated review on their pathology, diagnosis, mechanism, screening techniques, pharmacological, and future approaches. *Curr. Diabetes Rev.* **20**, e201023222416 (2024).
121. Islam, K. et al. Diabetes mellitus and associated vascular disease: pathogenesis, complications, and evolving treatments. *Adv. Ther.* **42**, 2659–2678 (2025).

122. Attiq, A., Afzal, S., Ahmad, W. & Kandeel, M. Hegemony of inflammation in atherosclerosis and coronary artery disease. *Eur. J. Pharmacol.* **966**, 176338 (2024).
123. Agarwala, A. et al. Biomarkers and degree of atherosclerosis are independently associated with incident atherosclerotic cardiovascular disease in a primary prevention cohort: the ARIC study. *Atherosclerosis* **253**, 156–163 (2016).
124. Pasut, A., Lama, E., Van Craenenbroeck, A. H., Kroon, J. & Carmeliet, P. Endothelial cell metabolism in cardiovascular physiology and disease. *Nat. Rev. Cardiol.* **22**, 923–943 (2025).
125. Umpierrez, G. E. et al. Hyperglycemic crises in adults with diabetes: a consensus report. *Diabetes Care* **47**, 1257–1275 (2024).
126. Sattar, N., Presslie, C., Rutter, M. K. & McGuire, D. K. Cardiovascular and kidney risks in individuals with type 2 diabetes: contemporary understanding with greater emphasis on excess adiposity. *Diabetes Care* **47**, 531–543 (2024).
127. Luo, J. et al. Features, functions, and associated diseases of visceral and ectopic fat: a comprehensive review. *Obesity* **33**, 825–838 (2025).
128. Sewaybricker, L. E., Huang, A., Chandrasekaran, S., Melhorn, S. J. & Schur, E. A. The significance of hypothalamic inflammation and gliosis for the pathogenesis of obesity in humans. *Endocr. Rev.* **44**, 281–296 (2023).
129. Choe, H. J., Almas, T., Neeland, I. J., Lim, S. & Després, J.-P. Obesity phenotypes and atherogenic dyslipidemias. *Eur. J. Clin. Invest.* <https://doi.org/10.1111/eci.70151> (2025).
130. Levelt, E. et al. Ectopic and visceral fat deposition in lean and obese patients with type 2 diabetes. *J. Am. Coll. Cardiol.* **68**, 53–63 (2016).
131. Taylor, R., Al-Mrabeh, A. & Sattar, N. Understanding the mechanisms of reversal of type 2 diabetes. *Lancet Diabetes Endocrinol.* **7**, 726–736 (2019).
This review discusses biological mechanisms underlying reversal of T2DM following weight loss.
132. Lim, S. & Meigs, J. B. Ectopic fat and cardiometabolic and vascular risk. *Int. J. Cardiol.* **169**, 166–176 (2013).
133. Piché, M.-E., Tchernof, A. & Després, J.-P. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ. Res.* **126**, 1477–1500 (2020).
134. Petersen, M. C. & Shulman, G. I. Mechanisms of insulin action and insulin resistance. *Physiol. Rev.* **98**, 2133–2223 (2018).
135. Chaurasia, B. & Summers, S. A. Ceramides — lipotoxic inducers of metabolic disorders. *Trends Endocrinol. Metab.* **26**, 538–550 (2015).
136. Blagov, A. et al. Mitochondrial dysfunction as a factor of energy metabolism disorders in type 2 diabetes mellitus. *Front. Biosci.* **16**, 5 (2024).
137. Pinti, M. V. et al. Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. *Am. J. Physiol. Endocrinol. Metab.* **316**, E268–E285 (2019).
138. Rovira-Llopis, S. et al. Mitochondrial dynamics in type 2 diabetes: pathophysiological implications. *Redox Biol.* **11**, 637–645 (2017).
139. Kuchay, M. S., Choudhary, N. S. & Ramos-Molina, B. Pathophysiological underpinnings of metabolic dysfunction-associated steatotic liver disease. *Am. J. Physiol. Cell Physiol.* **328**, C1637–C1666 (2025).
140. Steinberg, G. R., Valvano, C. M., De Nardo, W. & Watt, M. J. Integrative metabolism in MASLD and MASH: pathophysiology and emerging mechanisms. *J. Hepatol.* **83**, 584–595 (2025).
141. Larsson, S. C., Bäck, M., Rees, J. M. B., Mason, A. M. & Burgess, S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. *Eur. Heart J.* **41**, 221–226 (2020).
142. Sjöström, L. et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* **311**, 2297–2304 (2014).
143. Garvey, W. T. Long-term health benefits of intensive lifestyle intervention in the Look AHEAD study. *Obesity* **29**, 1242–1243 (2021).
This study highlights long-term health benefits of intensive lifestyle intervention in people with T2DM.
144. Wing, R. R.; Look AHEAD Research Group. Does lifestyle intervention improve health of adults with overweight/obesity and type 2 diabetes? Findings from the Look AHEAD randomized trial. *Obesity* **29**, 1246–1258 (2021).
145. Marso, S. P. et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* **375**, 1834–1844 (2016).
146. Bergman, M. et al. International Diabetes Federation position statement on the 1-hour post-load plasma glucose for the diagnosis of intermediate hyperglycaemia and type 2 diabetes. *Diabetes Res. Clin. Pract.* **209**, 111589 (2024).
147. Meijnikman, A. S. et al. Not performing an OGTT results in significant underdiagnosis of (pre)diabetes in a high risk adult caucasian population. *Int. J. Obes.* **41**, 1615–1620 (2017).
148. Holt, R. I. G. et al. The management of type 1 diabetes in adults. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **44**, 2589–2625 (2021).
149. Wagner, R. et al. Adult-onset type 1 diabetes: early detection, differential diagnosis, and emerging disease-modifying therapies. *Diabetes Res. Clin. Pract.* **231**, 113047 (2025).
150. Olesen, S. S., Toledo, F. G. S. & Hart, P. A. The spectrum of diabetes in acute and chronic pancreatitis. *Curr. Opin. Gastroenterol.* **38**, 509–515 (2022).
151. Fitipaldi, H. & Franks, P. W. Ethnic, gender and other sociodemographic biases in genome-wide association studies for the most burdensome non-communicable diseases: 2005–2022. *Hum. Mol. Genet.* **32**, 520–532 (2023).
152. Smith, K. et al. Multi-ancestry polygenic mechanisms of type 2 diabetes. *Nat. Med.* **30**, 1065–1074 (2024).
153. Udler, M. S. et al. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: a soft clustering analysis. *PLoS Med.* **15**, e1002654 (2018).
154. Dias, J.-A. et al. Evaluating multi-ancestry genome-wide association methods: statistical power, population structure, and practical implications. *Am. J. Hum. Genet.* **112**, 2493–2508 (2025).
155. Redondo, M. J. & Balasubramanyam, A. Toward an improved classification of type 2 diabetes: lessons from research into the heterogeneity of a complex disease. *J. Clin. Endocrinol. Metab.* **106**, e4822–e4833 (2021).
156. Redondo, M. J. et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol.* **6**, 361–369 (2018).
This study identifies novel subgroups of adult-onset diabetes through cluster analysis and links them to clinical outcomes.
157. Ahlqvist, E., Prasad, R. B. & Groop, L. Subtypes of type 2 diabetes determined from clinical parameters. *Diabetes* **69**, 2086–2093 (2020).
This study demonstrates the potential clinical utility of subtyping T2DM using routine clinical parameters.
158. Anjana, R. M. et al. Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study. *BMJ Open Diabetes Res. Care* **8**, e001506 (2020).
159. Sliker, R. C. et al. Replication and cross-validation of type 2 diabetes subtypes based on clinical variables: an IMI-RHAPSODY study. *Diabetologia* **64**, 1982–1989 (2021).
160. Zaharia, O. P. et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol.* **7**, 684–694 (2019).
161. Prasad, R. B. et al. Subgroups of patients with young-onset type 2 diabetes in India reveal insulin deficiency as a major driver. *Diabetologia* **65**, 65–78 (2022).
162. Schön, M. et al. Analysis of type 2 diabetes heterogeneity with a tree-like representation: insights from the prospective German diabetes study and the LURIC cohort. *Lancet Diabetes Endocrinol.* **12**, 119–131 (2024).
163. Dennis, J. M., Shields, B. M., Henley, W. E., Jones, A. G. & Hattersley, A. T. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol.* **7**, 442–451 (2019).
164. Gray, L. J. et al. The Leicester Risk Assessment score for detecting undiagnosed type 2 diabetes and impaired glucose regulation for use in a multiethnic UK setting. *Diabet. Med.* **27**, 887–895 (2010).
165. Barber, S. R., Dhalwani, N. N., Davies, M. J., Khunti, K. & Gray, L. J. External national validation of the Leicester self-assessment score for type 2 diabetes using data from the English Longitudinal Study of Ageing. *Diabet. Med.* **34**, 1575–1583 (2017).
This study validates the Leicester Self-Assessment risk score for T2DM in a national cohort.
166. Lindström, J. et al. The Finnish diabetes prevention study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* **26**, 3230–3236 (2003).
This trial shows that lifestyle intervention prevents progression to T2DM in individuals at high risk.
167. Chadha, C. et al. Reproducibility of a prediabetes classification in a contemporary population. *Metab. Open* **6**, 100031 (2020).
168. Wang, J. et al. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am. J. Clin. Nutr.* **60**, 23–28 (1994).
169. Aggarwal, R. et al. Diabetes screening by race and ethnicity in the United States: equivalent body mass index and age thresholds. *Ann. Intern. Med.* **175**, 765–773 (2022).
170. Tillin, T. et al. Ethnicity-specific obesity cut-points in the development of type 2 diabetes — a prospective study including three ethnic groups in the United Kingdom. *Diabet. Med.* **32**, 226–234 (2015).
171. Mayne, S. L., Auchincloss, A. H. & Michael, Y. L. Impact of policy and built environment changes on obesity-related outcomes: a systematic review of naturally occurring experiments. *Obes. Rev.* **16**, 362–375 (2015).
172. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the diabetes prevention program outcomes study. *Lancet Diabetes Endocrinol.* **3**, 866–875 (2015).
This trial confirms durable benefits of lifestyle and metformin on diabetes incidence and microvascular outcomes over 15 years.
173. Gong, Q. et al. Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. *Diabetologia* **54**, 300–307 (2011).
174. Gong, Q. et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the da qing diabetes prevention outcome study. *Lancet Diabetes Endocrinol.* **7**, 452–461 (2019).
This trial demonstrates sustained reductions in diabetes incidence and mortality after 30 years of lifestyle intervention.
175. Knowler, W. C. et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
176. Hamman, R. F. et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* **29**, 2102–2107 (2006).

177. Henson, J. et al. Waking up to the importance of sleep in type 2 diabetes management: a narrative review. *Diabetes Care* **47**, 331–343 (2024).
This paper reviews evidence showing that poor sleep quality and duration significantly affect blood glucose control and overall management of T2DM, highlighting sleep as a critical but often overlooked component of diabetes care.
178. Taheri, S. Sleep and cardiometabolic health—not so strange bedfellows. *Lancet Diabetes Endocrinol.* **11**, 532–534 (2023).
179. Jastreboff, A. M. et al. Tirzepatide for obesity treatment and diabetes prevention. *N. Engl. J. Med.* **392**, 958–971 (2025).
180. Riddle, M. C. et al. Consensus report: definition and interpretation of remission in type 2 diabetes. *Diabetes Care* **44**, 2438–2444 (2021).
181. Khunti, K., Papamargaritis, D., Aroda, V. R., Anjana, R. M. & Kashyap, S. R. Re-evaluating the concept of remission in type 2 diabetes: a call for patient-centric approaches. *Lancet Diabetes Endocrinol.* **13**, 615–634 (2025).
182. Rubino, F. et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol.* **13**, 221–262 (2025).
183. Kanbour, S., Ageeb, R. A., Malik, R. A. & Abu-Raddad, L. J. Impact of bodyweight loss on type 2 diabetes remission: a systematic review and meta-regression analysis of randomised controlled trials. *Lancet Diabetes Endocrinol.* **13**, 294–306 (2025).
184. Taheri, S. Type 2 diabetes remission: a new mission in diabetes care. *Diabetes Care* **47**, 47–49 (2023).
185. Khunti, K. et al. Glycaemic control is still central in the hierarchy of priorities in type 2 diabetes management. *Diabetologia* **68**, 17–28 (2025).
186. Powers, M. A. et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. *Diabetes Care* **43**, 1636–1649 (2020).
187. American Diabetes Association Professional Practice Committee. 5. Facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes — 2025. *Diabetes Care* **48**, S86–S127 (2024).
188. Zhao, F.-F., Suhonen, R., Koskinen, S. & Leino-Kilpi, H. Theory-based self-management educational interventions on patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *J. Adv. Nurs.* **73**, 812–833 (2017).
189. Bekele, B. B. et al. Effect of diabetes self-management education (DSME) on glycated hemoglobin (HbA1c) level among patients with T2DM: systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab. Syndr.* **15**, 177–185 (2021).
190. Davies, M. J. et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* <https://doi.org/10.1136/bmj.39474.922025.BE> (2008).
191. Chatterjee, S. et al. Diabetes structured self-management education programmes: a narrative review and current innovations. *Lancet Diabetes Endocrinol.* **6**, 130–142 (2018).
192. Philis-Tsimikas, A., Fortmann, A., Lleva-Ocana, L., Walker, C. & Gallo, L. C. Peer-led diabetes education programs in high-risk Mexican Americans improve glycaemic control compared with standard approaches: a project dulce promotora randomized trial. *Diabetes Care* **34**, 1926–1931 (2011).
193. Hadjiconstantinou, M. et al. Do web-based interventions improve well-being in type 2 diabetes? A systematic review and meta-analysis. *J. Med. Internet Res.* **18**, e270 (2016).
194. Barker, M. M. et al. User retention and engagement in the digital-based diabetes education and self-management for ongoing and newly diagnosed (myDESMOND) program: descriptive longitudinal study. *JMIR Diabetes* **8**, e44943 (2023).
195. Moschonis, G. et al. Effectiveness, reach, uptake, and feasibility of digital health interventions for adults with type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. *Lancet Digit. Health* **5**, e125–e143 (2023).
196. Philis-Tsimikas, A. et al. Dulce digital-me: results of a randomized comparative trial of static versus adaptive digital interventions for Latine adults with diabetes. *Ann. Behav. Med.* **59**, kaae077 (2025).
197. Gershkowitz, B. D., Hillert, C. J. & Crotty, B. H. Digital coaching strategies to facilitate behavioral change in type 2 diabetes: a systematic review. *J. Clin. Endocrinol. Metab.* **106**, e1513–e1520 (2021).
198. Shippee, N. D., Shah, N. D., May, C. R., Mair, F. S. & Montori, V. M. Cumulative complexity: a functional, patient-centered model of patient complexity can improve research and practice. *J. Clin. Epidemiol.* **65**, 1041–1051 (2012).
199. Boehmer, K. R. et al. Patient capacity and constraints in the experience of chronic disease: a qualitative systematic review and thematic synthesis. *BMC Fam. Pract.* **17**, 127 (2016).
200. May, C. R. et al. Rethinking the patient: using burden of treatment theory to understand the changing dynamics of illness. *BMC Health Serv. Res.* **14**, 281 (2014).
201. Sargeant, J. A. et al. A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. *Endocrinol. Metab.* **34**, 247–262 (2019).
202. Ahmad, E., Sargeant, J. A., Yates, T., Webb, D. R. & Davies, M. J. Type 2 diabetes and impaired physical function: a growing problem. *Diabetologia* **3**, 30–45 (2022).
203. Boulé, N. G., Haddad, E., Kenny, G. P., Wells, G. A. & Sigal, R. J. Effects of exercise on glycaemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* **286**, 1218–1227 (2001).
204. Rowlands, A. et al. Wrist-worn accelerometers: recommending ~ 1.0 mg as the minimum clinically important difference (MCID) in daily average acceleration for inactive adults. *Br. J. Sports Med.* **55**, 814–815 (2021).
205. Yates, T. et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. *Lancet* **383**, 1059–1066 (2014).
206. Homer, A. R. et al. Frequency of interruptions to sitting time: benefits for postprandial metabolism in type 2 diabetes. *Diabetes Care* **44**, 1254–1263 (2021).
207. Schwingshackl, L., Chaimani, A., Hoffmann, G., Schwedhelm, C. & Boeing, H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. *Eur. J. Epidemiol.* **33**, 157–170 (2018).
208. Lv, M. et al. Effects of vegetarian or vegan diets on glycaemic and cardiometabolic health in type 2 diabetes: a systematic review and meta-analysis. *Nutr. Rev.* **83**, 1438–1449 (2025).
209. Ajala, O., English, P. & Pinkney, J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am. J. Clin. Nutr.* **97**, 505–516 (2013).
210. Churuangsk, C. et al. Diets for weight management in adults with type 2 diabetes: an umbrella review of published meta-analyses and systematic review of trials of diets for diabetes remission. *Diabetologia* **65**, 14–36 (2022).
211. Liu, G. et al. Adherence to a healthy lifestyle in association with microvascular complications among adults with type 2 diabetes. *JAMA Netw. Open* **6**, e2252239 (2023).
212. Gidudu, M. et al. Factors affecting lifestyle modification among adults with type II diabetes mellitus attending care at Mbale regional referral hospital in Mbale City, Eastern Uganda: a mixed methods study. *J. Public Health Res.* **14**, 22799036251395268 (2025).
213. Davies, M. J. et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. *JAMA* **314**, 687–699 (2015).
214. Davies, M. et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* **397**, 971–984 (2021).
215. Garvey, W. T. et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* **402**, 613–626 (2023).
This trial shows that tirzepatide significantly improves weight loss and glycaemic outcomes in T2DM with obesity.
216. Lee, M. M. Y. et al. Cardiovascular and kidney outcomes and mortality with long-acting injectable and oral glucagon-like peptide 1 receptor agonists in individuals with type 2 diabetes: a systematic review and meta-analysis of randomized trials. *Diabetes Care* **48**, 846–859 (2025).
217. Hammad, B. F. et al. Exploring the multifaceted roles of GLP-1 receptor agonists: a comprehensive review. *Front. Clin. Diabetes Healthc.* **6**, 1590530 (2025).
218. Sanyal, A. J. et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N. Engl. J. Med.* **392**, 2089–2099 (2025).
219. Srinivasan, N. M., Farokhnia, M., Farinelli, L. A., Ferrulli, A. & Leggio, L. GLP-1 therapeutics and their emerging role in alcohol and substance use disorders: an endocrinology primer. *J. Endocr. Soc.* **9**, bvaf141 (2025).
220. Wharton, S. et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. *Postgrad. Med.* **134**, 14–19 (2022).
221. Azizi, Z., Rodriguez, F. & Assimes, T. L. Digital footprints of obesity treatment: GLP-1 receptor agonists and the health equity divide. *Circulation* **150**, 171–173 (2024).
222. Waldrop, S. W., Johnson, V. R. & Stanford, F. C. Inequalities in the provision of GLP-1 receptor agonists for the treatment of obesity. *Nat. Med.* **30**, 22–25 (2024).
223. Hussein, H. et al. Efficacy and tolerability of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a systematic review and network meta-analysis. *Diabetes Obes. Metab.* **22**, 1035–1046 (2020).
224. Kleinaki, Z., Kapnisi, S., Theodorelou-Charitou, S.-A., Nikas, I. P. & Paschou, S. A. Type 2 diabetes mellitus management in patients with chronic kidney disease: an update. *Hormones* **19**, 467–476 (2020).
225. Patel, S. M. et al. Sodium-glucose cotransporter-2 inhibitors and major adverse cardiovascular outcomes: a SMART-C collaborative meta-analysis. *Circulation* **149**, 1789–1801 (2024).
226. Banerjee, M., Pal, R., Nair, K. & Mukhopadhyay, S. SGLT2 inhibitors and cardiovascular outcomes in heart failure with mildly reduced and preserved ejection fraction: a systematic review and meta-analysis. *Indian Heart J.* **75**, 122–127 (2023).
227. Zannad, F. et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials. *Lancet* **396**, 819–829 (2020).
228. Mavrakanas, T. A., Tsoukas, M. A., Brophy, J. M., Sharma, A. & Gariani, K. SGLT-2 inhibitors improve cardiovascular and renal outcomes in patients with CKD: a systematic review and meta-analysis. *Sci. Rep.* **13**, 15922 (2023).
229. Ferrannini, E. Sodium-glucose co-transporters and their inhibition: clinical physiology. *Cell Metab.* **26**, 27–38 (2017).
230. Santos-Gallego, C. G. et al. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J. Am. Coll. Cardiol.* **73**, 1931–1944 (2019).
231. Vallon, V. & Verma, S. Effects of SGLT2 inhibitors on kidney and cardiovascular function. *Annu. Rev. Physiol.* **83**, 503–528 (2021).
232. Roberts, D. J. & Miyamoto, S. Hexokinase II integrates energy metabolism and cellular protection: acting on mitochondria and TORCing to autophagy. *Cell Death Differ.* **22**, 248–257 (2015).

233. Kanbay, M. et al. Effect of sodium-glucose cotransporter 2 inhibitors on hemoglobin and hematocrit levels in type 2 diabetes: a systematic review and meta-analysis. *Int. Urol. Nephrol.* **54**, 827–841 (2022).
234. Han, J. H. et al. The beneficial effects of empagliflozin, an SGLT2 inhibitor, on atherosclerosis in ApoE^{-/-} mice fed a western diet. *Diabetologia* **60**, 364–376 (2017).
235. Dihoum, A., Brown, A. J., McCrimmon, R. J., Lang, C. C. & Mordi, I. R. Dapagliflozin, inflammation and left ventricular remodelling in patients with type 2 diabetes and left ventricular hypertrophy. *BMC Cardiovasc. Disord.* **24**, 356 (2024).
236. Forrester, E. A. et al. Crucial role for sensory nerves and Na/H exchanger inhibition in dapagliflozin- and empagliflozin-induced arterial relaxation. *Cardiovasc. Res.* **120**, 1811–1824 (2024).
237. Kraus, B. J. et al. Characterization and implications of the initial estimated glomerular filtration rate ‘dip’ upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney Int.* **99**, 750–762 (2021).
238. Jongs, N. et al. Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor dapagliflozin in patients with CKD. *J. Am. Soc. Nephrol.* **33**, 2094–2107 (2022).
239. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**, 854–865 (1998).
240. Monami, M. et al. Effect of metformin on all-cause mortality and major adverse cardiovascular events: an updated meta-analysis of randomized controlled trials. *Nutr. Metab. Cardiovasc. Dis.* **31**, 699–704 (2021).
241. Charles, M. A. & Leslie, R. D. Diabetes: concepts of β-cell organ dysfunction and failure would lead to earlier diagnosis and prevention. *Diabetes* **70**, 2444–2456 (2021).
242. Zhu, M. et al. β Cell aging and age-related diabetes. *Aging* **13**, 7691–7706 (2021).
243. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes — 2025. *Diabetes Care* **48**, S181–S206 (2024).
244. Maiorino, M. I. et al. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care* **40**, 614–624 (2017).
245. Yang, R., Yang, Z., Chi, J. & Zhu, Y. Insulin delivery devices in diabetes management: applications and advancements. *Intell. Pharm.* **3**, 235–242 (2025).
246. Wysham, C. et al. Effect of insulin degludec vs insulin glargine u100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA* **318**, 45–56 (2017).
247. Philis-Tsimikas, A. et al. Rationale and design of the phase 3a development programme (ONWARDS 1-6 trials) investigating once-weekly insulin icodex in diabetes. *Diabetes Obes. Metab.* **25**, 331–341 (2023).
248. Bergenstal, R. M. et al. Once-weekly insulin efsitora alfa: design and rationale for the QWINT phase 3 clinical development programme. *Diabetes Obes. Metab.* **26**, 3020–3030 (2024).
249. Shetty, S. & Suvarna, R. Efficacy and safety of once-weekly insulin icodex in type 2 diabetes: a meta-analysis of ONWARDS phase 3 randomized controlled trials. *Diabetes Obes. Metab.* **26**, 1069–1081 (2024).
250. Bajaj, H. S. et al. Once-weekly insulin icodex compared with daily basal insulin analogues in type 2 diabetes: participant-level meta-analysis of the ONWARDS 1-5 trials. *Diabetes Obes. Metab.* **26**, 3810–3820 (2024).
251. Goldman, J., Triplitt, C. & Isaacs, D. Icodex: a novel once-weekly basal insulin for diabetes management. *Ann. Pharmacother.* **59**, 554–569 (2025).
252. Rosenstock, J. et al. Weekly fixed-dose insulin efsitora in type 2 diabetes without previous insulin therapy. *N. Engl. J. Med.* **393**, 325–335 (2025).
253. Wysham, C. et al. Insulin efsitora versus degludec in type 2 diabetes without previous insulin treatment. *N. Engl. J. Med.* **391**, 2201–2211 (2024).
254. Trevisan, R., Conti, M. & Ciardullo, S. Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes. *Diabetologia* **67**, 1480–1492 (2024).
255. Bajaj, H. S. et al. Continuous glucose monitoring-based metrics and hypoglycemia duration in insulin-experienced individuals with long-standing type 2 diabetes switched from a daily basal insulin to once-weekly insulin icodex: post hoc analysis of ONWARDS 2 and ONWARDS 4. *Diabetes Care* **47**, 729–738 (2024).
256. Philis-Tsimikas, A. et al. Once-weekly insulin efsitora alfa versus once-daily insulin degludec in adults with type 2 diabetes currently treated with basal insulin (QWINT-3): a phase 3, randomised, non-inferiority trial. *Lancet* **405**, 2279–2289 (2025).
257. Blevins, T. et al. Once-weekly insulin efsitora alfa versus once-daily insulin glargine U100 in adults with type 2 diabetes treated with basal and prandial insulin (QWINT-4): a phase 3, randomised, non-inferiority trial. *Lancet* **405**, 2290–2301 (2025).
258. Liu, Y. et al. Recent progress in glucose-responsive insulin. *Diabetes* **73**, 1377–1388 (2024).
259. Tomlinson, B., Patil, N. G., Fok, M., Chan, P. & Lam, C. W. K. The role of sulfonyleureas in the treatment of type 2 diabetes. *Expert Opin. Pharmacother.* **23**, 387–403 (2022).
260. Dormandy, J. A. et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAZone Clinical Trial in macroVascular Events): a randomised controlled trial. *Lancet* **366**, 1279–1289 (2005).
261. Kernan, W. N. et al. Pioglitazone after ischemic stroke or transient ischemic attack. *N. Engl. J. Med.* **374**, 1321–1331 (2016).
262. Li, C., Luo, J., Jiang, M. & Wang, K. The efficacy and safety of the combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors in type 2 diabetes mellitus: a systematic review and meta-analysis. *Front. Pharmacol.* **13**, 838277 (2022).
263. DeFronzo, R. A. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes. Metab.* **19**, 1353–1362 (2017).
264. Chen, B., Tao, L., Tian, M. & Ji, Z. Efficacy and safety of combination of semaglutide and basal insulin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Clin. Nutr. ESPEN* **66**, 564–572 (2025).
265. Amiel, S. A. The consequences of hypoglycaemia. *Diabetologia* **64**, 963–970 (2021).
266. Htoo, P. T. et al. Risk of severe hypoglycemia with newer second-line glucose-lowering medications in older adults with type 2 diabetes stratified by known indicators of hypoglycemia risk. *J. Gerontol. A* **78**, 2426–2434 (2023).
267. Zaccardi, F., Ling, S., Lawson, C., Davies, M. J. & Khunti, K. Severe hypoglycaemia and absolute risk of cause-specific mortality in individuals with type 2 diabetes: a UK primary care observational study. *Diabetologia* **63**, 2129–2139 (2020).
268. Zoungas, S. et al. Severe hypoglycemia and risks of vascular events and death. *N. Engl. J. Med.* **363**, 1410–1418 (2010).
269. Freckmann, G. et al. A comparative analysis of glycemic metrics derived from three continuous glucose monitoring systems. *Diabetes Care* **48**, 1213–1217 (2025).
270. Battelino, T. et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* **42**, 1593–1603 (2019).
271. Barchiesi, M. A. et al. Continuous glucose monitoring in type 2 diabetes: a systematic review of barriers and opportunities for care improvement. *Int. J. Qual. Health Care* **37**, mzaf046 (2025).
272. Espinoza, J., Xu, N. Y., Nguyen, K. T. & Klonoff, D. C. The need for data standards and implementation policies to integrate CGM data into the electronic health record. *J. Diabetes Sci. Technol.* **17**, 495–502 (2023).
273. Novo Nordisk. Novo Nordisk A/S: Wegovy approved in the US for the treatment of MASH. *Novo Nordisk* <https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=916416&s=09#> (15 August 2025).
274. Belfort, R. et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N. Engl. J. Med.* **355**, 2297–2307 (2006).
275. Cusi, K. et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann. Intern. Med.* **165**, 305–315 (2016).
276. Wei, Q., Xu, X., Guo, L., Li, J. & Li, L. Effect of SGLT2 inhibitors on type 2 diabetes mellitus with non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Front. Endocrinol.* **12**, 635556 (2021).
277. Lv, X. et al. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for the management of nonalcoholic fatty liver disease (NAFLD): a systematic review. *Endocrinol. Diabetes Metab.* **3**, e00163 (2020).
278. Rosenstock, J. et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* **398**, 143–155 (2021).
279. Packer, M. et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* **392**, 427–437 (2025).
280. Malhotra, A. et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N. Engl. J. Med.* **391**, 1193–1205 (2024).
281. Loomba, R. et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N. Engl. J. Med.* **391**, 299–310 (2024).
282. Nicholls, S. J. et al. Cardiovascular outcomes with tirzepatide versus dulaglutide in type 2 diabetes. *N. Engl. J. Med.* **393**, 2409–2420 (2025).
283. Phillips, L. S. et al. Clinical inertia. *Ann. Intern. Med.* **135**, 825–834 (2001).
284. Almigbal, T. H. et al. Clinical inertia in the management of type 2 diabetes mellitus: a systematic review. *Medicina* **59**, 182 (2023).
285. Khunti, K. & Davies, M. J. Clinical inertia — time to reappraise the terminology? *Prim. Care Diabetes* **11**, 105–106 (2017).
286. Khunti, K., Wolden, M. L., Thorsted, B. L., Andersen, M. & Davies, M. J. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care* **36**, 3411–3417 (2013).
287. Khunti, S., Khunti, K. & Seidu, S. Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia. *Ther. Adv. Endocrinol. Metab.* **10**, 2042018819844694 (2019).
- This review highlights the prevalence, causes and consequences of therapeutic inertia in T2DM and strategies to address it.**
288. Mauricio, D. et al. Change in insulin dose and HbA1c by geographical region — results from the diabetes unmet need with basal insulin evaluation (DUNE) study. *Diabetes* **67**, 1037-P (2018).
289. Shalaeva, E. V. et al. Impact of persistent medication adherence and compliance with lifestyle recommendations on major cardiovascular events and one-year mortality in patients with type 2 diabetes and advanced stages of atherosclerosis: results from a prospective cohort study. *Glob. Heart* **18**, 61 (2023).
290. Evans, M. et al. Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: a systematic literature review. *Diabetes Obes. Metab.* **24**, 377–390 (2022).
291. Polonsky, W. H. et al. Assessment of diabetes-related distress. *Diabetes Care* **18**, 754–760 (1995).
292. Konstantinou, P. et al. Barriers, facilitators, and interventions for medication adherence across chronic conditions with the highest non-adherence rates: a scoping review with recommendations for intervention development. *Transl. Behav. Med.* **10**, 1390–1398 (2020).

293. Wulandari, N., Lamuri, A., van Hasselt, F., Feenstra, T. & Taxis, K. The burden of depression among patients with type 2 diabetes: an umbrella review of systematic reviews. *J. Diabetes Complications* **39**, 109004 (2025).
294. Ascher-Svanum, H. et al. Associations between glycemic control, depressed mood, clinical depression, and diabetes distress before and after insulin initiation: an exploratory, post hoc analysis. *Diabetes Ther.* **6**, 303–316 (2015).
295. Lamptey, R., Berry, E., Hermanns, N. & Snoek, F. Editorial: highlights in diabetes self-management 2021/22. *Front. Clin. Diabetes Healthc.* **4**, 1116879 (2023).
296. Speight, J. et al. Bringing an end to diabetes stigma and discrimination: an international consensus statement on evidence and recommendations. *Lancet Diabetes Endocrinol.* **12**, 61–82 (2024).
This consensus statement provides evidence-based recommendations to address diabetes-related stigma and discrimination.
297. Speight, J., Conn, J., Dunning, T. & Skinner, T. C.; Diabetes Australia. Diabetes Australia position statement. A new language for diabetes: improving communications with and about people with diabetes. *Diabetes Res. Clin. Pract.* **97**, 425–431 (2012).
298. Bhattarai, M. et al. Association of sodium-glucose cotransporter 2 inhibitors with cardiovascular outcomes in patients with type 2 diabetes and other risk factors for cardiovascular disease: a meta-analysis. *JAMA Netw. Open* **5**, e2142078 (2022).
299. Undiagnosed type 2 diabetes: an invisible risk factor. *Lancet Diabetes Endocrinol.* **12**, 215 (2024).
300. Owolabi, M. O. et al. Gaps in guidelines for the management of diabetes in low- and middle-income versus high-income countries — a systematic review. *Diabetes Care* **41**, 1097–1105 (2018).
301. Sargeant, J. A. et al. Adults with early-onset type 2 diabetes (aged 18–39 years) are severely underrepresented in diabetes clinical research trials. *Diabetologia* **63**, 1516–1520 (2020).
302. Wang, M. C., Shah, N. S., Carnethon, M. R., O'Brien, M. J. & Khan, S. S. Age at diagnosis of diabetes by race and ethnicity in the United States from 2011 to 2018. *JAMA Intern. Med.* **181**, 1537–1539 (2021).
303. Paul, S. K. et al. Comparison of body mass index at diagnosis of diabetes in a multi-ethnic population: a case-control study with matched non-diabetic controls. *Diabetes Obes. Metab.* **19**, 1014–1023 (2017).
304. Xie, J. et al. Global burden of type 2 diabetes in adolescents and young adults, 1990–2019: systematic analysis of the Global Burden of Disease Study 2019. *BMJ* **379**, e072385 (2022).
305. Nanayakkara, N. et al. Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications: systematic review and meta-analyses. *Diabetologia* **64**, 275–287 (2021).
306. Goldney, J. et al. Age at onset of type 2 diabetes and prevalence of vascular disease and heart failure: systematic review and dose-response meta-analysis. *J. Diabetes Complications* **38**, 108849 (2024).
307. Barker, M. M. et al. Age at diagnosis of type 2 diabetes and depressive symptoms, diabetes-specific distress, and self-compassion. *Diabetes Care* **46**, 579–586 (2023).
308. Misra, S. et al. Managing early-onset type 2 diabetes in the individual and at the population level. *Lancet* **405**, 2341–2354 (2025).
309. Lim, L. L. et al. Aspects of multicomponent integrated care promote sustained improvement in surrogate clinical outcomes: a systematic review and meta-analysis. *Diabetes Care* **41**, 1312–1320 (2018).
310. Wagner, E. H. et al. Finding common ground: patient-centeredness and evidence-based chronic illness care. *J. Altern. Complement. Med.* **11**, S7–S15 (2005).
311. Amgen. Amgen announces robust weight loss with maritide in people living with obesity or overweight at 52 weeks in a phase 2 study. *Amgen* <https://go.nature.com/40esdb4> (2024).
312. Zhang, B. et al. Efficacy and safety of mazdutide in Chinese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 2 trial. *Diabetes Care* **47**, 160–168 (2024).
313. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/study/NCT04153929> (2022).
314. Rosenstock, J. et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *Lancet* **402**, 529–544 (2023).
This trial demonstrates potent metabolic effects of retatrutide, a triple GIP–GLP1–glucagon agonist, in T2DM.
315. Romero-Gómez, M. et al. A phase Ila active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease. *J. Hepatol.* **79**, 888–897 (2023).
316. Sanyal, A. J. et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N. Engl. J. Med.* **391**, 311–319 (2024).
317. Sanyal, A. J. et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat. Med.* **30**, 2037–2048 (2024).
This trial evaluates retatrutide in steatotic liver disease, highlighting potential benefits beyond glucose control.
318. Heymsfield, S. B. et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw. Open* **4**, e2033457 (2021).
319. McGowan, B. M. et al. Efficacy and safety of once-weekly semaglutide 2.4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. *Lancet Diabetes Endocrinol.* **12**, 631–642 (2024).
320. Eli Lilly and Company. Tirzepatide reduced the risk of developing type 2 diabetes by 94% in adults with pre-diabetes and obesity or overweight. *Eli Lilly* <https://go.nature.com/4b9JU0n> (2024).
321. Misra, S. et al. Precision subclassification of type 2 diabetes: a systematic review. *Commun. Med.* **3**, 138 (2023).
322. RADIANT Study Group. The rare and atypical diabetes network (RADIANT) study: design and early results. *Diabetes Care* **46**, 1265–1270 (2023).
323. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/study/NCT06603571> (2025).
324. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/study/NCT06373146> (2026).
325. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/study/NCT06565611> (2025).
326. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/study/NCT06564753> (2025).
327. Siminerio, L. M. The role of technology and the chronic care model. *J. Diabetes Sci. Technol.* **4**, 470–475 (2010).
328. NHS England. Quality and outcomes framework guidance for 2024/25. *NHS England* <https://www.england.nhs.uk/publication/quality-and-outcomes-framework-guidance-for-2024-25/> (2024).
329. Emonena, H. & Ojo, O. The efficacy of tele-monitoring in maintaining glycated haemoglobin levels in patients with type 2 diabetes mellitus: a systematic review. *Int. J. Env. Res. Public Health* **19**, 16722 (2022).
This systematic review finds telemonitoring to be effective in maintaining glycaemic control in T2DM.
330. Ni, K., Tampe, C. A., Sol, K., Cervantes, L. & Pereira, R. I. Continuous glucose monitor: reclaiming type 2 diabetes self-efficacy and mitigating disparities. *J. Endocr. Soc.* **8**, bvae125 (2024).
331. Ferreira, R. O. M. et al. Continuous glucose monitoring systems in noninsulin-treated people with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Technol. Ther.* **26**, 252–262 (2024).
332. Eeg-Olofsson, K. et al. Real-world study of flash glucose monitoring among adults with type 2 diabetes within the Swedish National Diabetes Register. *Diabetes Vasc. Dis. Res.* **20**, 14791641211067418 (2023).
333. Edelman, S., Cheatham, W. W., Norton, A. & Close, K. L. Patient perspectives on the benefits and challenges of diabetes and digital technology. *Clin. Diabetes* **42**, 243–256 (2024).
334. Cornelius, J., Doran, F., Jefford, E. & Salehi, N. Patient decision aids in clinical practice for people with diabetes: a scoping review. *Diabetol. Int.* **11**, 344–359 (2020).
335. Daly, A. & Hovorka, R. Technology in the management of type 2 diabetes: present status and future prospects. *Diabetes Obes. Metab.* **23**, 1722–1732 (2021).

Acknowledgements

The authors acknowledge M. Savage (Research Associate, Diabetes Research Centre, Leicester, UK), who provided considerable support with collating sections and formatting the final manuscript. The authors also acknowledge C. Franklin (Senior Creative, Diabetes Research Centre, Leicester, UK), who provided considerable support in drafting and amending the original figure concepts.

Author contributions

M.J.D. and S.L. are co-first authors. Introduction (all authors); Epidemiology (A.P.-T.); Mechanisms/pathophysiology (S.L., J.G. and T.S.); Diagnosis, screening and prevention (T.T.); Management (I.L., S.L., J.G., T.Y., D.R.F., A.P.-T. and M.J.D.); Quality of Life (R.L., J.G. and T.S.); Outlook (D.R.F., J.G. and R.L.); overview of Primer (M.J.D.).

Competing interests

M.J.D. has acted as a consultant/adviser and speaker for Eli Lilly and Company, Novo Nordisk and Sanofi, has attended advisory boards for AbbVie, Amgen, AstraZeneca, Biomea Fusion, Carmot/Roche, Daewoong Pharmaceutical, Sanofi, Zealand Pharma, Regeneron, GSK and EktaH and as a speaker for AstraZeneca, Boehringer Ingelheim and Zuellig Pharma. She has received grants from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. S.L. is an advisory board member for Novo Nordisk and AstraZeneca, and has served on the speakers' bureau of Novo Nordisk, Sanofi, Boehringer Ingelheim and AstraZeneca. He has received research funding from Chong Kun Dang and Daewoong Pharma. A.P.-T. performs research and serves as an adviser on behalf of their employer for Abbvie, Corcept, Dexcom, Eli Lilly and Company, Genentech, Medtronic, Novo Nordisk, Regeneron and Roche; there has been no direct or indirect transfer of funds. D.R.F. has served as an advisor to Eli Lilly and Company, Novo Nordisk, Abbott, Medtronic, AstraZeneca and Embecta, has received research support from Eli Lilly and Company and Novo Nordisk, and has received fees for speaking from AstraZeneca, Eli Lilly and Company, Abbott, Medtronic and Novo Nordisk. T.Y. has received investigator-initiated funding from AstraZeneca, contracted research funding from the Reinsurance Group of America and has acted as a consultant for Regeneron. I.L. received research funding (paid to institution) and/or product from Novo Nordisk, Boehringer Ingelheim, Dexcom, Roche, Pfizer and Eli Lilly and Company. I.L. received research-related consulting fees (paid to institution) from Novo Nordisk, advisory/consulting fees and/or other

support from Aadvark Therapeutics, Abbvie, Altimmune, Alveus Therapeutics, Amgen, Antag Therapeutics, AstraZeneca, Bain Capital, Bayer, Betagenon AB, Bioio, Biomea, Boehringer Ingelheim, Boston Scientific, Carmot, Corxel, Cytoki Pharma, Eli Lilly and Company, Genentech, Intercept, Janssen/J&J, Juvena, Keros Therapeutic, Mediflix, Merck, Metsera, Neurocrine, Novo Nordisk, Pfizer, Regeneron, Roche, Sanofi, Shionogi, Skye Bio, Source Bio, Structure Therapeutics, TERNs Pharma, The Comm Group, Verdiva Bio, WebMD and Zealand Pharma. T.T., R.L., T.S. and J.G. declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41572-026-00687-w>.

Peer review information *Nature Reviews Disease Primers* thanks P. Froguel, S. Cromer and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

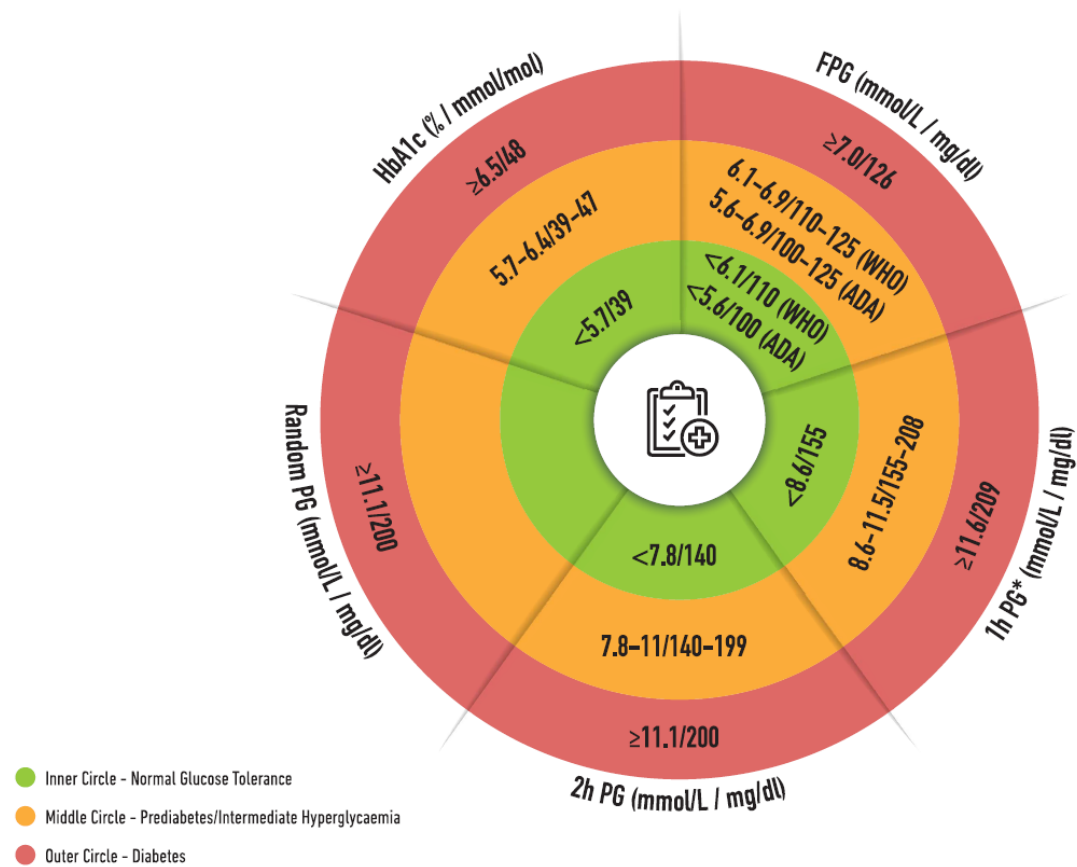
© Springer Nature Limited 2026

Supplementary information

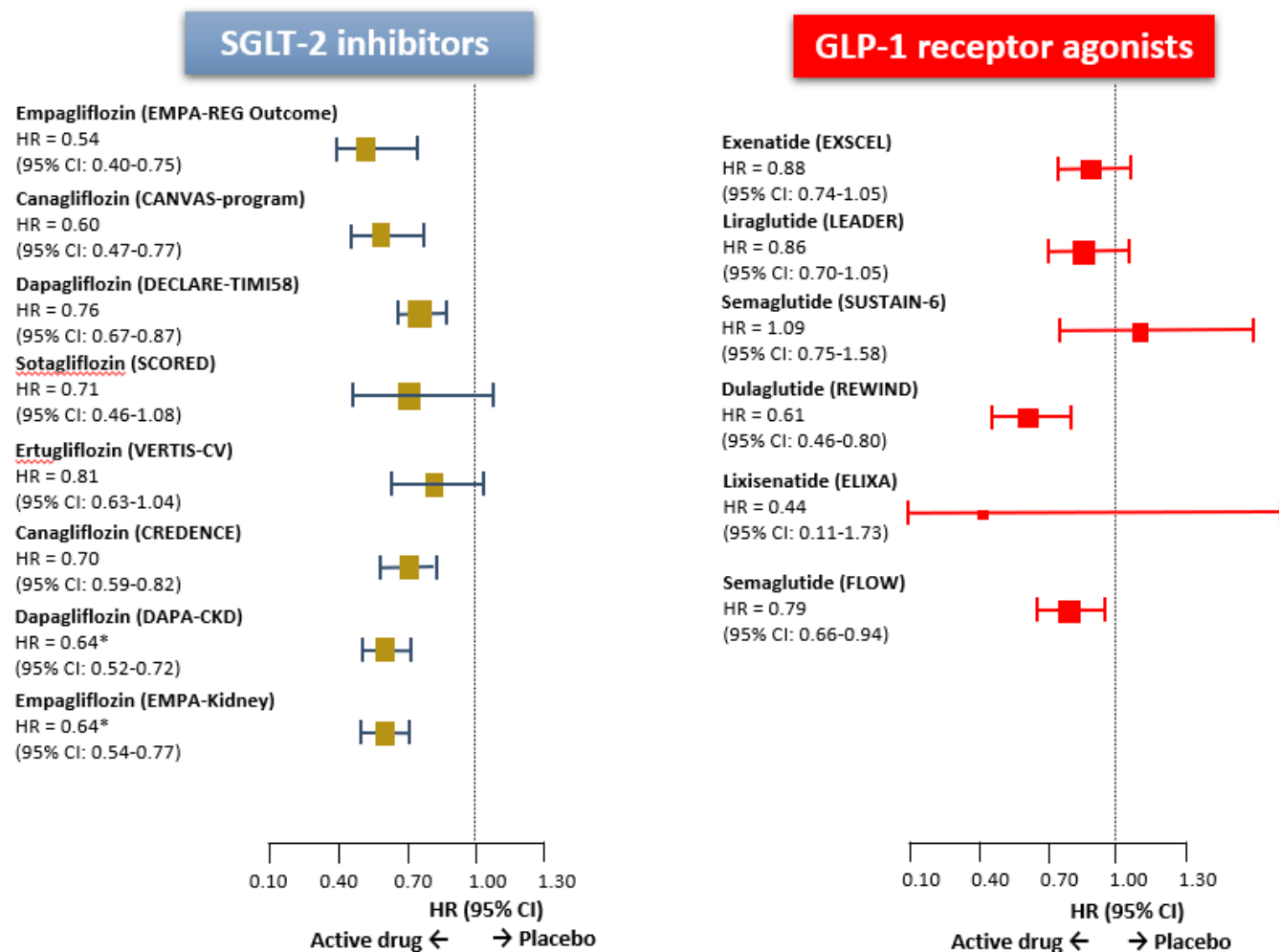
Type 2 diabetes mellitus

In the format provided by
the authors and unedited

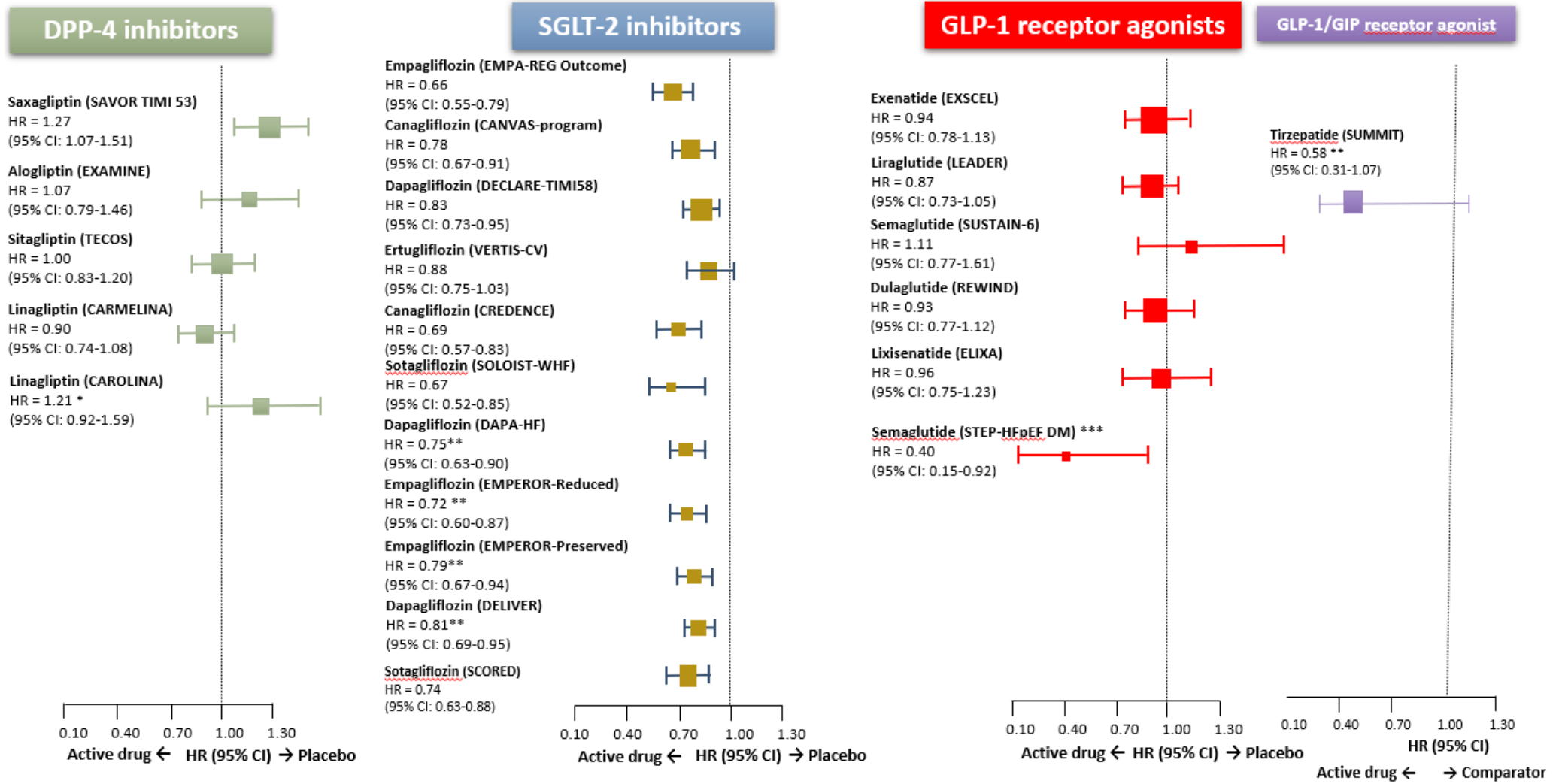
Supplementary Material



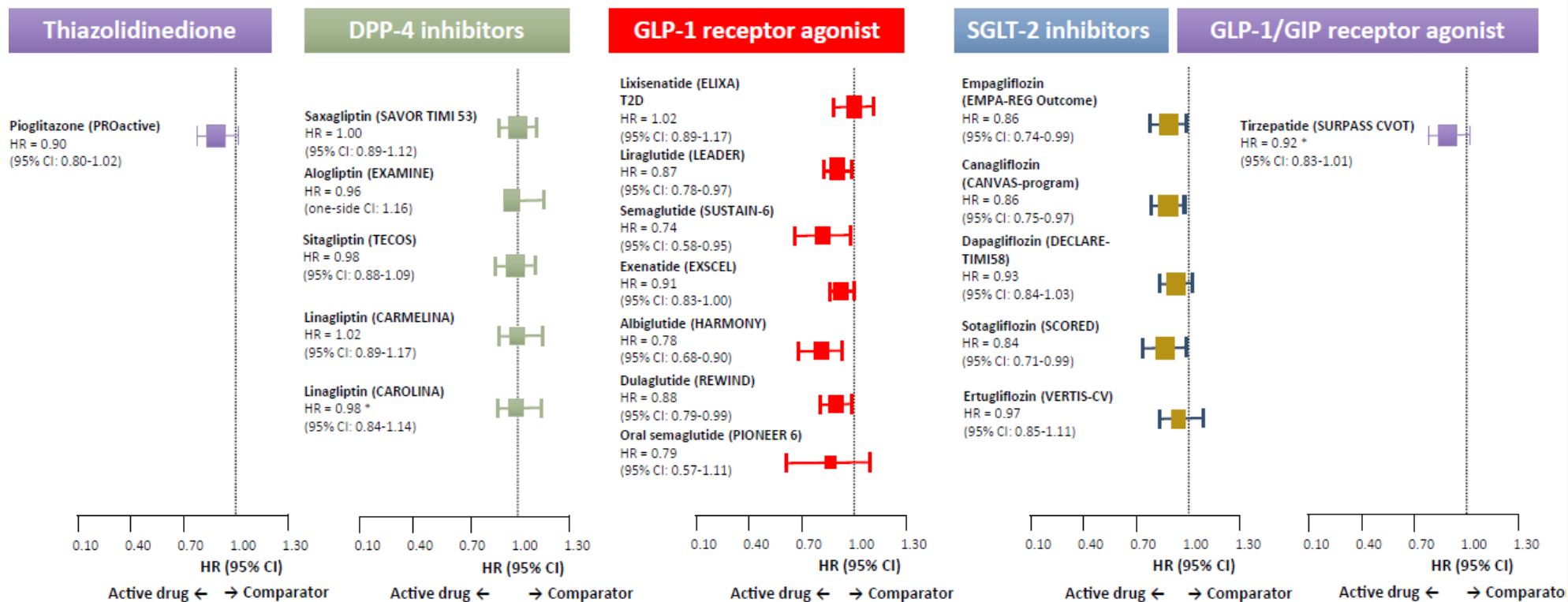
Supplementary Figure 1. Diagnostic criteria for T2DM, prediabetes (intermediate hyperglycaemia) and normal glucose tolerance. HbA1c=haemoglobin A1c. PG=plasma glucose. FPG=fasting plasma glucose. WHO=world health organisation. ADA=American diabetes association. *1h PG has been recommended as a diagnostic criteria for prediabetes and diabetes.



Supplementary Figure 2. Major trials reporting a composite renal outcome in people with T2DM. HR=hazard ratio. CI=confidence interval. All HRs represent the ratio of the rate of composite renal outcome with the specified medication, as compared to placebo. *The hazard ratio for DAPA-CKD presented is from the subgroup analysis involving only individuals with type 2 diabetes mellitus (T2DM). Similarly, the HR for EMPA-Kidney presented is from a subgroup analysis involving individuals with diabetes, of which the subtype was unspecified, however individuals with type 1 diabetes mellitus (T1DM) were not eligible for this trial.



Supplementary Figure 3. Major trials reporting heart failure outcomes in people with T2DM. HR=hazard ratio. CI=confidence interval. All HRs represent the ratio of the rate of heart failure outcomes with the specified medication, as compared to placebo. *This excludes CAROLINA (versus glimepiride). **HRs presented from the DAPA-HF; EMPEROR-Reduced; EMPEROR-Preserved; DELIVER; SUMMIT are in individuals with diabetes only from subgroup analysis. ***Hospitalisations or urgent heart failure visits were an exploratory endpoint, with fewer events in the STEP-HFpEF DM trial.



Supplementary Figure 4. Major trials reporting 3-point major cardiovascular event outcomes in people with T2DM. HR=hazard ratio. CI=confidence interval. All HRs represent the ratio of the rate of heart failure outcomes with the specified medication, as compared to placebo. *This excludes CAROLINA (versus glibemipride) and SURPASS CVOT (versus dulaglutide).

Supplementary Table 1. Medications with multi-system benefits in T2DM management. Source: Original.

		GLP1-based agent	SGLT2i	DPP4i	TZD	ACEi or ARB	Statins ± ezetimibe	Fibrates	EPA	nsMRA
Factors	Glucose or IR	↓↓	↓	↓	↓↓	Slightly↓	Slightly↑	Slightly↓	Slightly↓	-
	Blood pressure	↓	↓	-	-	↓↓	-	-	-	↓
	Obesity	↓↓	↓	-	↑	-	-	-	-	-
	Triglyceride	↓↓	↓	↓	↓↓	-	↓	↓↓	↓↓	-
	LDL-C	↓	↑	-	↑	-	↓↓	- or ↓	-	-
	HDL-C	↑	↑	-	↑	-	-	↑	↑	-
	Inflammation	↓	↓	↓	↓	↓	↓	↓	↓	↓
	Quality of gut microbiome	↑	↑	↑	-	-	-	-	↑	-
Target or organ	CVD	↓↓	↓↓	-	-	↓↓	↓↓	- or ↓	- or ↓	↓↓
	Stroke	↓↓	-	-	↓↓	↓↓	↓↓	- or ↓	- or ↓	↓
	CKD	↓	↓↓	- or ↓	-	↓↓	↓	↓	-	↓↓
	MASLD/MASH	↓↓	↓	-	↓↓	-	potential↓	-	↓	-
	Heart Failure	- or ↓	↓↓	- or ↑	↑	↓	-	-	-	-
Strengths		CV benefits in ASCVD Kidney benefits	CV benefits in HF, Kidney benefits	Albuminuria Reduction	CV benefits mainly in stroke	CV benefits, Kidney benefits	CV benefits	Diabetic microvascular complication↓	CV benefits	Kidney benefits, CV benefits
Adverse effects		GI adverse events	Genital tract infection↑ volume depletion, ketosis	HF risk↑ in saxagliptin	Weight gain, fluid retention, HF risk↑, osteoporosis risk↑	Cough by ACEi	Muscle-related side effect, glucose dysregulation, liver function abnormality	Transient eGFR ↓	Atrial fibrillation in high dose	Potassium ↑

Examples of medications	Exenatide, lixisenatide, dulaglutide, liraglutide, semaglutide, tirzepatide	dapagliflozin, empagliflozin, canagliflozin	Sitagliptin, vildagliptin, linagliptin, alogliptin, saxagliptin	Pioglitazone, rosiglitazone	Losartan, irbesartan, eprosartan, telmisartan, candesartan, fimasartan, olmesartan, azilsartan, enalapril, lisinopril, ramipril, captopril, quinapril, perindopril, trandolapril	Atorvastatin, rosuvastatin, simvastatin, fluvastatin, pravastatin, lovastatin, pitavastatin	fenofibrate, gemfibrozil	Icosapent ethyl	Finerenone
-------------------------	--	---	---	--------------------------------	--	---	-----------------------------	-----------------	------------

For factors ↑ represents an increase and ↓ represents a decrease in each parameter with medication use; For target organs, ↑ represents an increase in risk of adverse target organ outcome and ↓ represents a decrease (i.e., a protective effect). Double arrows represent a stronger effect size as compared to single arrows. – represents either no association or insufficient evidence. Note that the table is limited to medications developed over the last 50-years as the potential effect of medications developed prior to this period (e.g., metformin) mainly comes from observational evidence, rather than interventional.

GLP-1=glucagon-like peptide-1. IR=insulin resistance. LDL-C=low-density lipoprotein cholesterol. HDL-C=high-density lipoprotein cholesterol. ASCVD=atherosclerotic cardiovascular disease. CKD=chronic kidney disease. CV=cardiovascular. GI=gastrointestinal. HF=heart failure. eGFR=estimated glomerular filtration rate. DPP4i=Dipeptidyl peptidase-4 inhibitor. SGLT2i=Sodium/glucose co-transporter 2 inhibitor. TZD=thiazolidinediones. ACEi= angiotensin-converting-enzyme inhibitor. ARB=angiotensin receptor blocker. EPA= eicosapentaenoic acid. nsMRA= non-steroidal mineralocorticoid receptor antagonist.

Supplementary Table 2: Pharmacological Characteristics of pipeline GLP-1-based medication currently undergoing phase 3 trials for the treatment of T2DM and obesity.

Name	Molar mass	Feature	Dose	Bioavailability	Half-life	Ref.
Orfoglipron (LY-3502970)	882.97 g/mol	Oral, non-peptide, small molecule, GLP-1RA	9, 15, 27, or 45 mg	20-40%	25-68 hours	¹⁻³
Maridebart cafraglutide (MariTide) (AMG 133)	4600.70 g/mol	Agonist of GLP-1R and antagonist of GIPR (monoclonal antibody)	21 to 840 mg	NA	16.5-23.8 days	⁴
Cagrilintide/semaglutide (Cagrisema) (NN-9388)	31,200 g/mol + 4113.64 g/mol	Amylin and GLP-1 receptors dual agonist	Cagrilintide 2.4 mg/ semaglutide 2.4 mg	Cagrilintide 30% ⁵ / semaglutide 89%	Cagrilintide 159-195 hours / semaglutide 145- 165 hours	⁶
Survodutide (BI 456906)	4231.69 g/mol	Glucagon/GLP-1 receptors dual agonist	0.45, 1.8, 2.4, 3.0, or 4.8 mg	93% ⁷	100 hours	⁸
Mazdutide (IBI362 or LY3305677)	4476.06 g/mol	Glucagon/GLP-1 receptors dual agonist	3.0, 4.5, or 6.0 or 9.0 mg	NA	7.3–44.8 days	^{9,10}
Retatrutide (LY-3437943)	4845.44 g/mol	GLP-1, GIP, and glucagon receptors triple agonist	1, 3, 8, or 12 mg	NA	6 days	^{11,12}
Ecnoglutide (XW003)	4284.76 g/mol	GLP-1 receptor agonist	1.2, 1.8, or 2.4 mg	NA	5.2 to 6.8 days	¹³
RA, receptor agonist; Ref., reference; NA, not available.						

Trials shown are the medication with phase 3 trials underway at the date of submission: 28th August 2025

Supplementary Table 3: Efficacy of pipeline GLP-1-based medication currently undergoing phase 3 trials for glucose management: the data thus far

Name	Doses tested	Weeks (primary)	Age (years ± SD)	% Female	Baseline weight & BMI (kg ± SD / kg·m ² ± SD)	Baseline HbA1c (% ± SD)	HbA1c reduction (%; 95% CI*)	Weight reduction (% -unless otherwise stated; 95% CI)	Trial details	Reference
Orforglipron (LY-3502970)	3, 12, 36 mg SC QD	40	53.8 ± 11.8	51.1	90.2 ± 23.1 / 33.0 ± 7.5	7.99 ± 0.89	-1.48 (-1.66, 1.96) with 36mg vs -0.41 (-0.60, -0.22) with placebo	-7.6 (-8.8, -6.4) with 36mg vs -1.7 (-2.6, -0.8) with placebo	ACHIEVE-1, phase 3 (NCT05971940)	¹⁴
Mazdutide (IBI362)	4, 6 mg SC QW	24	50.4 ± NR	NR	77.7 ± NR/ NR	8.24% ± NR	-2.15 (SE 0.109) with 6 mg vs -0.14 (SE 0.107) with placebo	-7.8 (SE 0.47) with 6mg vs -1.3 (SE 0.46) with placebo	DREAMS-1, phase 3 (NCT05643961)	¹⁵
CagriSema (NN-9388)	2.4 mg semaglutide + 2.4 mg cagrilintide SC QW	32	58 ± 9	36%	105.7 ± 24.1 / 35.5 ± 6.3	8.4 ± 0.8	-2.2 (SE 0.15) with 2.4 mg/ 2.4 mg vs -1.8 (SE 0.16) with	-15.6 (SE 1.26) with 2.4 mg/ 2.4 mg vs -5.1 (SE 1.26) with 2.4 mg semaglutide vs	Phase 2 (NCT04982575)	¹⁶

Name	Doses tested	Weeks (primary)	Age (years ± SD)	% Female	Baseline weight & BMI (kg ± SD / kg·m ² ± SD)	Baseline HbA1c (% ± SD)	HbA1c reduction (%; 95% CI*)	Weight reduction (% -unless otherwise stated; 95% CI)	Trial details	Reference
							2.4 mg semaglutide vs -0.9 (SE 0.15) with 2.4mg cagrilintide	-8.1 (SE 1.23) with 2.4mg cagrilintide		
Survodutide (BI 456906)	0.3, 0.9, 1.8, 2.7 QW; 1.2, 1.8 mg SC BIW	16	57.3 ± 9.8	43.3	96.6 ± 21.6 / 33.9 ± 6.0	8.07 ± 0.84	-1.68 (-1.91, -1.45) with 1.8mg BIW Vs -0.15 (-0.35, 0.05) with placebo	-8.7% (-10.1, -7.3) with 1.8mg BIW Vs -5.3% (-6.6, -4.1) with 1mg semaglutide (Placebo NR)	Phase 2 (NCT04153929)	¹⁷
Retatrutide (LY-3437943)	0.5, 4 (with dose escalation), 4 (no dose escalation), 8 (slow escalation), 8 (fast escalation). 12 mg SC QW	24 (36 for extension)	56.2 ± 9.7	56	98.2 ± 21.1 / 35.0 ± 6.3	8.3 ± 1.1	At 36 weeks: -2.16 (SE 0.13) with 12mg Vs	At 36 weeks: -16.94 (SE 1.30) with 12mg Vs -3.00 (SE 0.86) with placebo	Phase 2 (NCT04867785)	¹⁸

Name	Doses tested	Weeks (primary)	Age (years ± SD)	% Female	Baseline weight & BMI (kg ± SD / kg·m ² ± SD)	Baseline HbA1c (% ± SD)	HbA1c reduction (%; 95% CI*)	Weight reduction (% -unless otherwise stated; 95% CI)	Trial details	Reference
							-0.30 (SE 0.24) with placebo			
Ecnoglutide (XW003)	0.4, 0.8, 1.2 mg SC QW	20	50.2 ± 9.62	32.1	74.0 ± 13.4 / 26.2 ± 3.4	8.59 ± 0.72	Vs -2.39 (SE 0.15) with 1.2 mg Vs -0.55 (SE 0.15) with placebo	-2.26kg (CI NR) with 1.2 mg Vs 0.50 (CI NR) with placebo	Phase 2 (CTR20211014)	¹⁹

*95% CI presented unless other measure of variance presented

SD: Standard deviation; BMI: Body mass index; CI: Confidence interval; QD: Once daily; QW: Once weekly; NR: Not reported; SE: Standard error; BIW: Bi-weekly; SC: Subcutaneous

Trials shown are the medication with phase 3 trials underway at the date of submission: 28th August 2025

Supplementary Table 4: Efficacy of pipeline GLP-1-based medication currently undergoing phase 3 trials for weight management in individuals with T2DM: the data thus-far

Name	Doses tested	Weeks (primary)	Age (years ± SD)	% Female	Baseline weight & BMI (kg ± SD / kg·m ² ± SD)	Baseline HbA1c (% ± SD)	Weight reduction (%; 95% CI)	HbA1c reduction (%; 95% CI)	Trial details	Reference
Orforglipron (LY-3502970)	6, 12, 36 mg PO QD	72 weeks	NR	NR	101.4 ± NR / NR	8.1 ± NR	-10.5 (CI NR) with 36mg Vs -2.2 (CI NR) with placebo	-1.8 (CI NR) with 36mg Vs -0.1 (CI NR) with placebo	ATTAIN-2, phase 3 (NCT05872620)	²⁰
Maritide (AMG 133; maridebart cafraglutide)	140, 280, 420 mg SC Q4W	52	55.1 ± 11.2	42	103.9 ± 21.7 / 36.5 ± 7.0	7.9 ± 0.7	-12.3 (-15.3, -9.2) with 420 mg Vs -1.7 (-2.9, -0.6) with placebo	-1.5 (-1.9, -1.0) Vs -0.1 (-0.4, -0.5) with placebo	Phase 2 (NCT05669599)	²¹
CagriSema (cagrilintide + semaglutide)	2.4 mg + 2.4 mg SC QW	68	56.0 ± NR	47.2%	102.2 ± NR / 36.2 ± NR	8.0 ± NR	-13.7 (CI NR) with 2.4/2.4mg Vs -3.4 (CI NR) with placebo	-1.8 (CI NR) with 2.4/2.4mg Vs -0.4 (CI NR) with placebo	REDEFINE-2, phase 3a (NCT05394519)	²²

SD: Standard deviation; BMI: Body mass index; CI: Confidence interval; QD: Once daily; QW: Once weekly; NR: Not reported; SE: Standard error; BIW: Bi-weekly; SC: Subcutaneous; PO: Oral

Trials shown are the medication with phase 3 trials underway at the date of submission: 28th August 2025

References for supplementary material

1. Pratt, E. *et al.* Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes. *Diabetes Obes Metab* **25**, 2642–2649 (2023).
2. Kawai, T. *et al.* Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. *Proc Natl Acad Sci U S A* **117**, 29959–29967 (2020).
3. Ono, R. *et al.* A phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of danuglipron (PF-06882961), an oral small-molecule glucagon-like peptide-1 receptor agonist, in Japanese adults with type 2 diabetes mellitus. *Diabetes Obes Metab* **25**, 805–814 (2023).
4. Véniant, M. M. *et al.* A GIPR antagonist conjugated to GLP-1 analogues promotes weight loss with improved metabolic parameters in preclinical and phase 1 settings. *Nat Metab* **6**, 290–303 (2024).
5. Kruse, T. *et al.* Development of Cagrilintide, a Long-Acting Amylin Analogue. *J Med Chem* **64**, 11183–11194 (2021).
6. Enebo, L. B. *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial. *Lancet* **397**, 1736–1748 (2021).
7. Thomas, L. *et al.* The dual GCGR/GLP-1R agonist survodutide: Biomarkers and pharmacological profiling for clinical candidate selection. *Diabetes Obes Metab* **26**, 2368–2378 (2024).
8. Zimmermann, T. *et al.* BI 456906: Discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy. *Mol Metab* **66**, 101633 (2022).
9. Ji, L. *et al.* Safety and efficacy of a GLP-1 and glucagon receptor dual agonist mazdutide (IBI362) 9 mg and 10 mg in Chinese adults with overweight or obesity: A randomised, placebo-controlled, multiple-ascending-dose phase 1b trial. *EClinicalMedicine* **54**, 101691 (2022).

10. Jiang, H. *et al.* A phase 1b randomised controlled trial of a glucagon-like peptide-1 and glucagon receptor dual agonist IBI362 (LY3305677) in Chinese patients with type 2 diabetes. *Nat Commun* **13**, 3613 (2022).
11. Abdul-Rahman, T. *et al.* The power of three: Retatrutide's role in modern obesity and diabetes therapy. *Eur J Pharmacol* **985**, 177095 (2024).
12. Coskun, T. *et al.* LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. *Cell Metab* **34**, 1234-1247.e9 (2022).
13. Guo, W. *et al.* Discovery of ecnoglutide - A novel, long-acting, cAMP-biased glucagon-like peptide-1 (GLP-1) analog. *Mol Metab* **75**, 101762 (2023).
14. Rosenstock, J. *et al.* Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes. *N Engl J Med* (2025) doi:10.1056/NEJMoa2505669.
15. ZHU, D. *et al.* 306-OR: Mazdutide vs. Placebo as Monotherapy in Patients with Type 2 Diabetes (DREAMS-1). *Diabetes* **74**, 306-OR (2025).
16. Frias, J. P. *et al.* Efficacy and safety of co-administered once-weekly cagrilintide 2·4 mg with once-weekly semaglutide 2·4 mg in type 2 diabetes: a multicentre, randomised, double-blind, active-controlled, phase 2 trial. *Lancet* **402**, 720–730 (2023).
17. Blüher, M., Rosenstock, J., Hoefler, J., Manuel, R. & Hennige, A. M. Dose-response effects on HbA1c and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial. *Diabetologia* **67**, 470–482 (2024).
18. Rosenstock, J. *et al.* Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *Lancet* **402**, 529–544 (2023).

19. Zhu, D. *et al.* Efficacy and safety of GLP-1 analog ecnoglutide in adults with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 2 trial. *Nat Commun* **15**, 8408 (2024).
20. Lilly's oral GLP-1, orforglipron, is successful in third Phase 3 trial, triggering global regulatory submissions this year for the treatment of obesity | Eli Lilly and Company.
<https://investor.lilly.com/news-releases/news-release-details/lillys-oral-glp-1-orforglipron-successful-third-phase-3-trial>.
21. Jastreboff, A. M. *et al.* Once-Monthly Maridebart Cafraglutide for the Treatment of Obesity - A Phase 2 Trial. *N Engl J Med* (2025) doi:10.1056/NEJMoa2504214.
22. Davies, M. J. *et al.* Cagrilintide-Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes. *N Engl J Med* **393**, 648–659 (2025).