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The *Lancet* Commission on diabetes: using data to transform diabetes care and patient lives

Juliana C N Chan†, Lee-Ling Lim, Nicholas J Wareham*, Jonathan E Shaw*, Trevor J Orchard*, Ping Zhang*, Eric S H Lau, Björn Eliasson*, Alice P S Kong*, Majid Ezzati*, Carlos A Aguilar-Salinas*, Margaret McGill*, Naomi S Levitt*, Guang Ning*, Wing-Yee So*, Jean Adams, Paula Bracco, Nita G Forouhi, Gabriel A Gregory, Jingchuan Guo, Xinyang Hua, Emma L Klatman, Dianna J Magliano, Boon-Peng Ng, David Ogilvie, Jenna Panter, Meda Pavkov, Hui Shao, Nigel Unwin, Martin White, Constance Wou, Ronald C W Ma*, Maria I Schmidt*, Ambady Ramachandran*, Yutaka Seino*, Peter H Bennett*, Brian Oldenburg*, Juan José Gagliardino*, Andrea O Y Luk*, Philip M Clarke*, Graham D Ogle*, Melanie J Davies*, Rury R Holman*, Edward W Gregg‡*

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*Members of the *Lancet* Commission on diabetes

†Commission chair

‡Commission co-chair

Executive summary

2020 will go down in history as the year when the global community was awakened to the fragility of human health and the interdependence of the ecosystem, economy, and humanity. Amid the COVID-19 pandemic, the vulnerability of people with diabetes during a public health emergency became evident by their at least 2 times increased risk of severe disease or death, especially in individuals with poorly controlled diabetes, comorbidities, or both. The disease burden caused by COVID-19, exacerbated by chronic conditions like diabetes, has inflicted a heavy toll on health-care systems and the global economy.

In this *Lancet* Commission on diabetes, which embodies 4 years of extensive work on data curation, synthesis, and modelling, we urge policy makers, payers, and planners to collectively change the ecosystem, build capacity, and improve the clinical practice environment. Such actions will enable practitioners to systematically collect data during routine practice and to use these data effectively to diagnose early, stratify risks, define needs, improve care, evaluate solutions, and drive changes at patient, system, and policy levels to prevent and control diabetes and other non-communicable diseases. Emerging evidence regarding the possible damaging effects of severe acute respiratory syndrome coronavirus 2 on pancreatic islets implies the potential worsening of the COVID-19 pandemic and the diabetes epidemic, adding to the urgency of these collective actions.

Prevention, early detection, prompt diagnosis, and continuing care with regular monitoring and ongoing evaluation are key elements in reducing the growing burden of diabetes. Given the silent and progressive nature of diabetes, it is epidemiological analyses that have provided a framework for identifying populations and subgroups at risk of diabetes and its complications. Although the total prevalence of diabetes reflects disease burden, incidence rates might reflect the effects of interventions among determinant factors that include, but are not limited to, political, socioeconomical, and technological changes within a population, area, or both.

In 2019, 463 million people had diabetes worldwide, with 80% from low-income and middle-income countries. Over 70% of global deaths are due to non-communicable diseases, including diabetes, cardiovascular disease, cancer, and respiratory disease. On average, diabetes reduces life expectancy in people aged 40–60 years by 4–10 years and independently increases the risk of death

Key messages

- Ensuring access to insulin, patient education, and tools for monitoring blood glucose concentration can prevent premature deaths and emergencies in young patients with type 1 diabetes, especially in disadvantaged communities
- The effects of maternal hyperglycaemia on childhood obesity require a multicomponent life-course strategy to prevent young-onset diabetes, which might benefit the next generation
- Complex causes, notably psychosocial needs, especially in patients with young-onset diabetes, call for structured assessment to personalise care for reducing premature development of non-communicable diseases and death
- The diverse environmental, behavioural, and socioeconomic causes of type 2 diabetes require a multitiered societal and population-based prevention strategy
- The marked differences in diabetes diagnosis, treatment, and outcomes in low-income and middle-income countries versus those in high-income countries are likely to be due to differences in investment, capacity, health-care systems, and care organisation
- Sustained reduction of common cardiometabolic risk factors, including smoking cessation and use of statins, renin–angiotensin system inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonist therapies can reduce cardiovascular–renal diseases and all-cause death in patients with type 2 diabetes
- The delivery of team-based care can enable systematic collection of data during routine clinical practice to improve the quality of electronic medical records and to establish registers for surveillance, prevention, and treatment
- The strengthening of existing infrastructures to provide continuing integrated care and the creation of career paths for physicians with knowledge and skills to reorganise diabetes care, train non-physician personnel, and use technology effectively can improve the accessibility, sustainability, and affordability of diabetes prevention and care

Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (Prof J C N Chan FRCP, L-L Lim PhD, E S H Lau PhD, Prof A P S Kong FRCP, W-Y So FRCP, Prof R C W Ma FRCP, A O Y Luk MD); **Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China** (Prof J C N Chan, Prof A P S Kong, W-Y So, Prof R C W Ma, A O Y Luk); **Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China** (Prof J C N Chan, Prof A P S Kong, W-Y So, Prof R C W Ma, A O Y Luk); **Asia Diabetes Foundation, Hong Kong Special Administrative Region, China** (Prof J C N Chan, L-L Lim, E S H Lau, A O Y Luk); **Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia** (L-L Lim); **Medical Research Council Epidemiology Unit, Institute of Metabolic Science, University of Cambridge School of Clinical Medicine, Cambridge, UK** (Prof N J Wareham FMedSci, J Adams PhD, Prof N G Forouhi PhD, D Ogilvie PhD, J Panter PhD, Prof N Unwin FFPH, Prof M White MD, C Wou MPhil); **Baker Heart and Diabetes Institute, Melbourne, VIC, Australia** (Prof J E Shaw FRACP, Prof D J Magliano PhD); **School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof J E Shaw, Prof D J Magliano); **School of Life Sciences, La Trobe University, Melbourne, VIC, Australia** (Prof J E Shaw); **Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, KS, USA** (Prof T J Orchard MMedSci, J Guo PhD); **Division of Diabetes Translation, US Centers for Disease Control and Prevention, Atlanta, GA, USA** (P Zhang PhD, B-P Ng PhD, M Pavkov PhD, H Shao PhD, Prof E W Gregg PhD); **Institute of Medicine, Sahlgrenska Academy, University of**

from cardiovascular disease, renal disease, and cancer by 1·3–3·0 times. Diabetes is among the leading causes of non-traumatic lower extremity amputation and blindness, especially in people of working age. The co-occurrence of these morbidities severely impairs quality of life, reduces productivity, and causes major suffering.

By revisiting the definition of an epidemic, we explain how the concept of environment–agent–host interactions, which is often used to explain marked variations in risk exposure and outcomes in communicable diseases, also applies to diabetes, in which ecosystem and human behaviours are key upstream factors. In this light, we highlight the effects of maternal hyperglycaemia on adolescent obesity, and the emerging epidemic of young-onset diabetes due to multiple causes and its high risk of premature death and complications. Apart from ageing, environmental factors, and socioeconomic factors, notable underlying risk associations of diabetes are poor nutrition, physical inactivity, depression, poverty, and low educational attainment, especially in underserved communities. The multidimensional nature of these risk factors calls for a wide-ranging society–population–community strategy to integrate prevention, diagnosis, and care of patients with type 2 diabetes.

Despite the availability of efficacious medications proven to reduce cardiovascular–renal events and death rates in clinical trial settings, their scarce provision and access to trained health-care providers, together with inefficient care organisation, have prevented the translation of evidence-based, risk-reducing therapies to clinical practice in most care settings. Even with the availability of essential medications, the complex phenotypes and multiple needs of individuals with diabetes require a systematic approach to stratify risk, classify disease subtypes, identify specific needs, and personalise care. Regarding type 1 diabetes, we present the continuing high standardised mortality ratios, especially in individuals living in deprived communities, and low-income and middle-income countries. Poor access to life-saving technologies, including insulin and tools for monitoring blood glucose concentration, and inadequate education for self-management have resulted in many avoidable deaths and acute emergencies in these young patients.

On the basis of best evidence and practices, we summarise the benefits of more effectively managing multiple risk factors in patients with diagnosed diabetes whereby (1) sustained weight reduction in patients with obesity by 15 kg or more can induce remission of type 2 diabetes for up to 2 years; (2) reducing glycated haemoglobin A_{1c} (HbA_{1c}) by 0·9% (10 mmol/mol), systolic blood pressure by 10 mm Hg, or LDL cholesterol concentration by 1 mmol/L (39 mg/dL) can independently reduce the risk of cardiovascular disease, all-cause death, or both, by 10–20% in patients with type 2 diabetes; (3) reducing multiple risk factors, including by use of statins and renin–angiotensin system inhibitors, can prevent cardiovascular–renal events by 20–40% in individuals with or at risk of having diabetes; (4) use of SGLT2 inhibitors and GLP-1 receptor agonists can reduce cardiovascular–renal events and death rates by up to 40%, independent of their effect on lowering blood glucose concentration; (5) use of data-driven, team-based integrated care through the reorganisation of health-care provision can reduce cardiovascular and all-cause death in patients with type 2 diabetes by 20–60%; and (6) implementing a structured lifestyle intervention and use of metformin can each prevent or delay type 2 diabetes in individuals with impaired glucose tolerance by 30–50%.

To translate these evidence-based strategies for reducing risk of diabetes and its complications, we put together an implementation plan showing that by training non-physician personnel to form diabetes teams, health-care providers can redesign workflow and use information and communication technology to set up diabetes registers, and use the data collected to empower self-management, improve provider–patient communication, and reduce multiple risk factors. With this multicomponent strategy, health-care providers can identify patients with type 1 diabetes and young-onset diabetes who are at high risk of acute and long-term complications, as well as individuals with comorbidities, atypical diabetes, and complex needs who require interdisciplinary management with ongoing support. With prospectively designed and unified data management systems, key stakeholders (including health-care planners and providers) can support the collective needs of clinical, surveillance, and research activities related to diabetes, and create societal impact by transforming care and informing policies.

By use of modelling, we have compared the estimated effects of our proposed integrated actions with the effects of current fragmented actions. In high-income countries, the standardised mortality ratio for patients with type 1 diabetes is 2·5, compared with that of 4·9–33·9 in low-income and middle-income countries. In 2017, 1·1 million young patients worldwide were diagnosed with type 1 diabetes under the age of 20 years and an estimated 14 466 individuals aged younger than 25 years died. If all patients with type 1 diabetes had received comprehensive care based on international guidelines and had been ensured access to intensive insulin therapy, personalised education, and regular complications assessments, we estimate that 12 092 of these deaths could have been averted. In 2017, 217 million individuals with type 2 diabetes (aged 30–69 years) lived in ten low-income and middle-income countries. Of these individuals, 3·2 million patients are estimated to have died after 3 years, with 1·3 million of these deaths due to cardiovascular disease. If access to essential medications had been ensured and control of blood pressure, HbA_{1c}, and LDL cholesterol concentration had been improved in 70% of diagnosed patients, we estimate that 800 000 of these premature deaths might have been prevented.

If a society–population–community strategy was implemented aiming to reduce illiteracy and social disparity, and create a health-enabling environment supported by a community-based, health-promoting policy linked to an integrated care system, the occurrence of 11 065 cases of diabetes and 6617 cardiovascular events in the next 5 years for a population of 1 million people in China could be potentially averted. After 20 years, 33 773 cases of diabetes and 51 863 cardiovascular events could be averted. These figures would translate to 44 million fewer cases of diabetes and 67 million fewer cardiovascular events in the Chinese population of 1·3 billion people compared with status quo.

To close the gaps in diabetes prevention, care, data, and professional knowledge (panel 1), we recommend the establishment of a global taskforce for diabetes and non-communicable diseases (NCDs), led by policy makers and consisting of stakeholders across different sectors, including, but not limited to, health-care institutions, academia, school, industry, professional bodies or experts, and non-governmental organisations. Such a taskforce can design, steer, and support a multi-component strategy to address the multidimensional nature of diabetes and other NCDs. This strategy is in line with the UN Sustainable Development Goals (SDGs), WHO NCD Global Monitoring Framework, WHO Convention Framework for Tobacco Control, and professional practice guidelines.

Introduction

According to WHO, diabetes is diagnosed either by a fasting plasma glucose concentration equal to or more than 7·0 mmol/L (126 mg/dL), 2 h plasma glucose concentration equal to or more than 11·1 mmol/L (200 mg/dL) during a 75 g oral glucose tolerance test, HbA_{1c} equal to or more than 6·5% (48 mmol/mol), or a combination of all three.[1] Diabetes is a heterogeneous condition with complex causes including, but not limited to, environmental, lifestyle, and genetic factors. Most affected individuals (95%) have type 2 diabetes, characterised by various combinations of insulin resistance and insulin deficiency. In this Commission, the term diabetes refers to chronic hyperglycaemia fulfilling these criteria, irrespective of the cause (unless otherwise stated).

Over the past several decades, the scientific community has amassed a large body of knowledge about the increasing health and socioeconomic burden of type 2 diabetes and its multidimensional nature. There is now strong evidence indicating that type 2 diabetes is preventable and might be reversed by adopting healthy lifestyles and sustained weight reduction. Diabetes and its complications are also treatable by ensuring continuous access to attentive and well organised care, structured patient education, and medications. In some areas where data are available, the incidence of diabetes and its complications are decreasing;[2] however, major gaps in care, data, and outcomes still exist, especially in low-income and middle-income countries (LMICs). In these countries, insufficient infrastructure and capacity, high costs of medications, fragmentation of health-care systems, health illiteracy, and social disparity are major barriers, resulting in many individuals with type 1 or type 2 diabetes not being diagnosed, treated, or managed. Despite increasing health-care investment in high-income countries (HICs), similar barriers are faced by underserved populations within these countries.

The global epidemics of diabetes and obesity epitomise the interlinking nature of individuals, communities, and societies in which ageing, poor nutrition, and physical inactivity are major drivers. In LMICs, other factors, such as environmental pollution, food insecurity, and social disparity, might also contribute. If diabetes develops and is not adequately managed, its lifelong nature can have an enormous impact on individuals, families, and society. Given that WHO's definition of health is "a state of physical, mental and social wellness",[3] diabetes is a prime example of how societal factors can become essential players in disease development, which in turn affects individuals, families, and society. This Commission argues that by implementing what we have learned to benefit people with or at risk of having diabetes, we can save a huge amount of unnecessary costs and burden for individuals, families, and society.

The Commission

In 2016, 26 experts in public health, clinical care, epidemiology, and health economics were brought together by *The Lancet* to review the evidence and knowledge gaps in diabetes; to develop strategic and actionable plans (ie, actions); and to estimate the effects of no action versus action, with a focus on LMICs. In this evidence-based Commission, we have highlighted what is known and not known, agreed and disagreed, achieved and not achieved. We have emphasised the importance of building infrastructures, capacity, and processes to deliver evidence-based, structured diabetes care and education programmes with ongoing, systematic data collection to drive actions at the practice, system, and policy levels. We have indicated societal barriers, such as policies, poverty, and politics, that contribute to the scarce provision and poor access to quality preventive care. The consequences are escalating and unsustainable health-care costs due to complications from diabetes, which are often preventable in the first place, not only in LMICs but also in HICs.

To address these challenges, we have provided a framework in which, by redesigning care settings, workflow, and team structure, we can implement an integrated diabetes detection, prevention, and management plan to reduce the incidence of diabetes-related complications and type 2 diabetes in individuals at high risk. These measures must be supported by intersectoral policies to mitigate the negative effects of societal determinants and to create long-term benefits. With use of data from epidemiological studies, clinical trials, and

Gothenburg, Gothenburg, Sweden (Prof B Eliasson PhD); **Department of Endocrinology and Metabolism, Sahlgrenska University Hospital, Gothenburg, Sweden** (Prof B Eliasson); **Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK** (Prof M Ezzati FMedSci, Prof E W Gregg); **Medical Research Council Centre for Environment and Health, Imperial College London, London, UK** (Prof M Ezzati); **WHO Collaborating Centre on NCD Surveillance and Epidemiology, Imperial College London, London, UK** (Prof M Ezzati); **Departamento de Endocrinología y Metabolismo, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico** (Prof C A Aguilar-Salinas PhD); **Diabetes Centre, Royal Prince Alfred Hospital, University of Sydney, Sydney, NSW, Australia** (M McGill MSc); **Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Medicine and Health Sciences, University of Cape Town, Cape Town, South Africa** (Prof N S Levitt FRCP); **Shanghai Clinical Center for Endocrine and Metabolic Disease, Department of Endocrinology, Ruijin Hospital, Shanghai Jiaotong University, School of Medicine, Shanghai, China** (Prof G Ning PhD); **Shanghai Institute of Endocrine and Metabolic Diseases, Shanghai, China** (Prof G Ning); **School of Medicine and Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil** (P Bracco PhD, Prof M I Schmidt PhD); **Life for a Child Program, Diabetes NSW and ACT, Glebe, NSW, Australia** (G A Gregory BSc, E L Klatman MSc, Prof G D Ogle FRACP); **Sydney Medical School, University of Sydney, Sydney, NSW, Australia** (G A Gregory); **Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK** (X Hua PhD, Prof P M Clarke PhD); **College of Nursing and Disability, Aging and Technology Cluster, University of Central Florida, Orlando, FL, USA** (B-P Ng); **India Diabetes Research Foundation and Dr A Ramachandran's**

Diabetes Hospitals, Chennai, India (Prof A Ramachandran FRCP); **Center for Diabetes, Endocrinology and Metabolism, Kansai Electric Power Hospital, Osaka, Japan** (Prof Y Seino PhD); **Yutaka Seino Distinguished Center for Diabetes Research, Kansai Electric Power Medical Research Institute, Kobe, Japan** (Prof Y Seino); **Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ, USA** (P H Bennett FRCP); **Nossal Institute for Global Health, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia** (Prof B Oldenburg PhD); **WHO Collaborating Centre on Implementation Research for Prevention and Control of NCDs, University of Melbourne, Melbourne, VIC, Australia** (Prof B Oldenburg); **Centro de Endocrinología Experimental y Aplicada, UNLP–CONICET–CICPBA, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, La Plata, Argentina** (Prof J J Gagliardino PhD); **National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia** (Prof G D Ogle); **Diabetes Research Centre, University of Leicester, Leicester, UK** (Prof M J Davies FRCP); **and Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK** (Prof R R Holman FMedSci)

Correspondence to:
Prof Juliana C N Chan, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China
jchan@cuhk.edu.hk

or

Prof Edward W Gregg, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London W2 1PG, UK
e.gregg@imperial.ac.uk

***Panel 1*: Recommendations**

1. Closing the gap in diabetes prevention

We recommend that policy makers, planners, and managers implement context-relevant policies through intersectoral, interdepartmental, and interdisciplinary collaborations aimed at:

- Strengthening educational, environmental, and social–health–medical systems to improve literacy, protect the environment, reduce social disparity, and ensure access to continuing care
- Creating a smoke-free, health-enabling environment that promotes healthy eating and physical activity to reduce the number of people with obesity and diabetes in the community
- Promoting use of non-physician personnel, assisted by information and communications technology, to implement lifestyle intervention programmes and to reduce the risk of type 2 diabetes in individuals at high risk, with linkage to a prepared health-care system for managing people detected with undiagnosed diabetes and for individuals who have been diagnosed
- Aligning the expectations of care providers, industry, and payers to ensure access, affordability, and sustainability of continuing care for people with or at risk of diabetes

2. Closing the professional knowledge gap in diabetes

We recommend that universities, accreditation bodies, and professional organisations train knowledge workers, and that funding agencies support research programmes on diabetes, especially in low-income and middle-income countries, aimed at:

- Redesigning the curriculum for undergraduate students of social, health, and medical disciplines to better enable workforces to provide the acute and long-term health-care needs of people with or at risk of diabetes and other non-communicable diseases
- Organising continuous professional training courses and conferences to update knowledge and skills, including the appropriate use of diagnostic tools, medications, and technologies for diabetes prevention and care
- Developing diabetes as a specialty health-care discipline essential for maintaining care standards, translating evidence into practice, and providing training on the job
- Promoting research programmes focused on the design, implementation, and evaluation of the delivery of diabetes care and prevention programmes in a naturalistic environment

3. Closing the gap in diabetes care

We recommend that policy makers, payers, and planners increase investments in diabetes care, focused on the prevention of complications, by strengthening health-care systems by:

- Establishing hospital-based and community-based diabetes centres and teams, including professional and non-physician personnel (eg, trained community health workers or peers) to provide continuing care to people with or at risk of developing diabetes
- Ensuring that all individuals with type 1 diabetes are registered and have access to insulin, equipment for self-monitoring blood glucose concentration, and appropriate health education to promote self-management
- Redesigning workflow and implementing a team approach to collect data systematically during clinical practice to create registers for providing the information required to stratify risk, identify needs, empower self-management, enhance patient–provider communication, personalise care, and recall defaulters
- Collecting essential data regularly for quality assurance (eg, control of cardiometabolic risk factors, renal function, use of organ protective drugs, and self-management)
- Leveraging existing facilities and workforces and providing career advancement for health-care providers specialised in diabetes to scale up the delivery of data-driven, team-based integrated care

4. Closing the data gap in diabetes

We recommend that public health workers, health-care providers, and researchers, with administrative support, work collaboratively and use registers, administrative data, and audits to complement data from randomised controlled trials to inform decision making at patient, provider, and system levels by:

- Integrating and analysing these databases to facilitate the monitoring of prevalence (disease burden) and incidence (effects of intervention) of diabetes and its complications
- Analysing this real-world evidence to evaluate the effectiveness of new interventions and technologies, and to develop more sophisticated outcome models to project cost-effectiveness within different subpopulations in naturalistic environments to better inform decision making
- Detecting population trends of diabetes and its complications, and emerging unmet needs to guide practice and policies

real-world settings, we have modelled the short-term (1–3 years), mid-term (10 years), and long-term (20 years) effects of implementing a multicomponent strategy, including societal measures aimed at reducing the burden of diabetes and other NCDs, which could save millions of deaths and billions of dollars in LMICs.

This Commission provides a data-driven argument for members of the public, patients, practitioners, payers, and policy makers that, despite the daunting nature of diabetes and other NCDs, there are numerous solutions to avert the grave consequences of this global epidemic. Implementing these solutions will require a collective transformation of our ecosystem and health-care environment in pursuit of adherence to evidence-based professional guidelines, WHO NCD Global Monitoring Framework, WHO Convention Framework for Tobacco Control, and UN SDGs for our society, community, and humanity.

Provision of quality diabetes care can greatly reduce the burden of this NCD

Globally, 70% of all deaths are due to four NCDs: diabetes, cardiovascular disease (including mainly ischaemic heart disease and stroke), cancer, and respiratory disease, with diabetes increasing the risk of death from cardiovascular disease, renal disease, and cancer by 1·3–3·0 times.[4] In 2019, 463 million individuals were affected by diabetes.[5] In a worldwide trend analysis, the prevalence of diabetes has doubled in men and increased by 60% in women over the past 25 years.[6] Estimates from the USA and Australia indicate that diabetes reduces life expectancy by at least 6 years when diagnosed at age of 40 years and by at least 4 years when diagnosed at the age of 60 years,[7–9] with childhood-onset type 1 diabetes having an even greater impact in the absence of adequate care.[10] In China, a man diagnosed with diabetes in the year 2000 at the age of 50 years lost, on average, 9 years of life compared with age-matched individuals without diabetes.[11]

Diabetes confers a 2·3 times increased risk of cardiovascular disease,[12] and 30% of individuals with diabetes die from cardiovascular disease.[13] In resource-limited settings, acute medical crises, such as diabetic ketoacidosis or hyperglycaemic hyperosmolar states, are important causes of death. In Mexico and China, deaths due to a hyperglycaemic crisis made up 8–10% of all deaths in individuals with diabetes, compared with less than 1% in the UK.[11,14,15] During the COVID-19 pandemic, patients with diabetes have had at least 2 times increased risk of severe disease (including death) compared with individuals without diabetes, especially among patients with poor glycaemic control, multiple risk factors, or diabetes-related complications.[16,17] Despite the silent nature of diabetes, the COVID-19 global emergency has exposed the vulnerability of these individuals with heavy tolls on health-care systems, economies, and humanity.[18]

Deaths from cardiovascular disease, renal disease, and cancer

In the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, after accounting for multicausality, 63% (10·8 million deaths, 95% CI 10·1–11·5) from cardiovascular–renal diseases in 2010 were attributable to the combined effect of high blood pressure, blood glucose concentration, serum cholesterol concentration, and body-mass index (BMI), compared with 67% (7·1 million [6·6–7·6]) of deaths from similar causes in 1980.[19] In the Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017), smoking, high systolic blood pressure and plasma glucose concentration, alcohol use, and history of preterm birth in men, and high systolic blood pressure, plasma glucose concentration, and BMI in women were leading risk factors in terms of attributable disability-adjusted life-years (DALYs).[20] In the USA, the incidence of diabetes-related complications has decreased during the past two decades; however, this decrease has been much slower for end-stage kidney disease than for cardiovascular disease.[21] In the US Renal Register, the proportion of patients with end-stage kidney disease due to diabetes has risen steadily and is presently at around 47%.[22] This rising trend might be due to improved survival from cardiovascular insults in individuals with diabetes, which has given kidney disease more opportunities to evolve.[23]

The high incidence of cancer as a cause of death in people with diabetes was recognised as early as 1914.[24] With ageing and improved prevention of and survival from cardiovascular disease, there is an increase in this double burden of diabetes and cancer. Even after adjustment for shared risk factors (eg, age, obesity, and smoking), diabetes increases the relative risk for all-site cancer (except for prostate cancer) by 1·2–2·0 times, compared with the general population.[4,25] Although the mechanisms underlying the close association between diabetes and cancer need further elucidation, the increased risk of cancer in type 1 diabetes[26] and the independent associations between blood glucose concentration and cancer risk[27] support an important role of the dysregulation of glucose metabolism in this risk association. In a 2018 analysis, 5·6% of all incident cancers in 2012 were attributable to the combined effects of diabetes and high BMI as independent risk factors, corresponding to 792 600 new cases.[28]

Diabetic foot and eye complications

In a systematic review of 35 population-based studies, with diabetic retinopathy ascertained from retinal photographs, the overall prevalence was 34·6% for any diabetic retinopathy, 7·0% for proliferative diabetic retinopathy, 6·8% for diabetic macular oedema, and 10·2% for vision-threatening diabetic retinopathy.[29] These figures implied an estimated global burden of 93 million individuals with diabetic retinopathy and 28 million individuals with sight-threatening stages of diabetic retinopathy in 2010.[29] In another systematic review of eight prospective population-based studies on diabetic retinopathy, the annual incidence of the condition was 2·2–12·7% with an annual progression of 3·4–12·3%, without sex differences. Although hypertension was not reported as a clinically significant risk factor, suboptimal glycaemic control increased the risk of diabetic retinopathy by 10–40%.[30] Individuals with diabetes are 7–30 times more likely to have non-traumatic lower extremity amputations than are the general population, accounting for over half of all such amputations.[31,32] Good podiatry care often prevents limb amputation and people who need amputation usually have disseminated vascular disease that contributes to their poor survival rate. In high-income areas such as North America, Europe, and Australia, the incidence of lower extremity amputation among individuals with diabetes has fallen over the past decade.[21,31] The updated estimates of incidence of lower

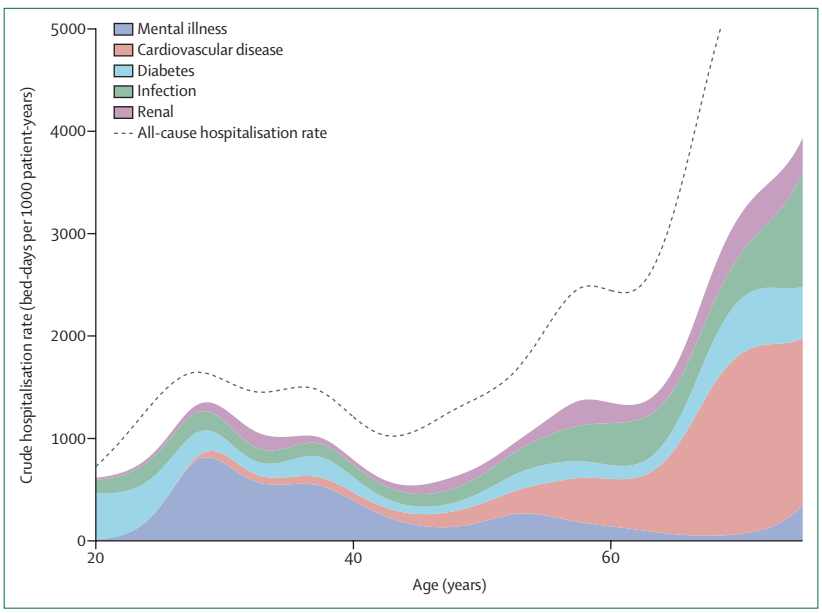

Figure 1: **Crude hospitalisation rates for selected principal diagnoses among people with young-onset type 2 diabetes in the Hong Kong Diabetes Register**
These rates show the excess burden of hospitalisation and mental illness. Reproduced from Ke et al,[42] by permission of American College of Physicians.

extremity amputation ranged between 1·9 and 3·9 per 1000 person-years in Europe and the USA.[32–34] However, the latest analysis of national data in the USA suggests resurgence of non-traumatic lower extremity amputation in young (aged 18–44 years) and middle-aged (aged 45–64 years) populations between 2009 and 2015.[35]

Diabetes, comorbidities, and mental health: impact on patients and caregivers

Individuals with diabetes are twice as likely to have depression than is the general population, a condition often under-recognised and untreated.[36,37] Similarly, individuals with depression are more likely to develop diabetes.[38] Apart from environmental stressors (eg, socioeconomic deprivation and life events), diabetes and depression might share common behavioural risk factors (eg, smoking and unhealthy lifestyles) and biological mechanisms driven by maternal and perinatal adversity, chronic hypothalamic–pituitary–adrenal axis dysregulation, sleep disruptions, sympathetic overactivity, and cytokine-mediated inflammation.[39] A diagnosis of diabetes calls for changes in lifestyle, long-term use of medications, and regular visits to health-care providers. These demands on daily life might contribute to the high prevalence of anxiety, stress, depression, or a combination of all three, affecting between a third and a fifth of individuals with type 2 diabetes.[38] These negative emotions can set up a self-perpetuating cycle of suboptimal self-care and treatment non-adherence, frequent hypoglycaemic and hyperglycaemic episodes, and poor clinical outcomes.[40,41]

In a report that used registers and population-based electronic medical records of 420 000 Chinese adults with incident type 2 diabetes observed between 2002 and 2014, data modelling indicated that patients with young-onset type 2 diabetes diagnosed before the age of 40 years spent an average of 100 days in hospital from diagnosis to the age of 75 years, with a third of the hospitalisations due to mental illness before the age of 40 years (figure 1).[42] The frequent clustering of multiple morbidities increases the complexity of managing type 2 diabetes. In the UK, by use of the Clinical Practice Research Datalink, researchers analysed the co-occurrence of 18 chronic conditions (including diabetes) and reported that patients living in the most deprived areas had more comorbidities that frequently clustered with depression, especially in women, than did patients living in affluent areas.[43] With data on demographics, comorbidities, and disease duration in patients with type 2 diabetes, researchers from Singapore reported five clusters of comorbidities. One cluster included high prevalence of depression in women aged younger than 65 years with short-to-moderate disease duration. Another cluster included men and women aged 65 years and older with moderate-to-long disease duration and multiple morbidities.[44] These two patient groups had the highest health-care utilisation.

In addition to this challenge is the growing burden of cognitive decline and dementia in diabetes.[45] The presence of these comorbidities does not only affect the quality of life of the patient but also markedly increases the emotional burden on caregivers, which is amplified by poor access and continuity of care, and insufficient communication among different service providers and specialties. Although there are examples of good practice often due to the behaviour of individual physicians, a system-wide approach requiring improved communication and care coordination is needed to address the physical and emotional needs of patients and their caregivers.[46]

Young-onset diabetes requires improved risk stratification and disease classification

In general, young-onset diabetes is defined as diabetes diagnosis before the age of 40 years. From 1980 to 2014, the global age-standardised prevalence of diabetes in adults aged 20 years and older increased from 4·3% (95% CI 2·4–7·0) to 9·0% (7·2–11·1) in men, and from 5·0% (2·9–7·9) to 7·9% (6·4–9·7) in women. These trends were driven largely by ageing and worsening risk factors, notably obesity, as well as decreasing death rates among individuals with diabetes in some countries. During the same period, the age-standardised prevalence in adults of working age (20–64 years) has increased from 3·2% (1·6–5·8) to 7·8% (6·1–10·0) in men, and from 3·9% (2·0–6·8) to 6·8% (5·3–8·5) in women.[6] In some communities (eg, Native Americans), there was a rise in the total prevalence of diabetes in children and adolescents, mostly attributed to type 2 diabetes.[47]

Young-onset diabetes increases risk of premature death, morbidities, and hospitalisations

In the early 1970s, Pima Indians diagnosed with type 2 diabetes before the age of 25 years were reported to have high rates of morbidities (eg, end-stage kidney disease, amputation, blindness) and death after an average of 15–20 years duration of diabetes.[48,49] Similar findings were also reported in Japanese patients with young-onset diabetes (aged <40 years), who had higher rates of diabetic nephropathy than did adults with type 1 diabetes.[50,51] In Hong Kong, the rising incidence of type 1 and type 2 diabetes in people under the age of 40 years[52] concurred with the most rapid rate of increase in renal replacement therapy in the age group of 45–65 years.[53] In the clinic-based Joint Asia Diabetes Evaluation (JADE) Register, a fifth of adults with diabetes in Asia had young-onset diabetes.[54] In a survey of 420 000 Chinese adults with diabetes under public care, patients with young-onset diabetes had the highest hospitalisation rates at any attained age with risk ratios of 1·8 for all-cause admissions, 6·7 for renal disease, 3·7 for diabetes, 2·1 for cardiovascular disease, and 1·7 for infection, compared with late-onset diabetes.[42]

The high prevalence of complications in young-onset diabetes is driven mainly by a long disease duration.[55] Mortality rate ratios are consistently higher in younger age groups (aged <50 years) than in age-matched individuals without diabetes, partly because of their low background mortality (figure 2).[11,14,56] In the USA, a temporal decrease in the rates of cardiovascular disease and related deaths among older individuals (aged 65–74 years and ≥75 years) with diabetes was far less evident in younger patients (aged 20–44 years and 45–64 years).[21] In the Swedish National Diabetes Register, patients with type 2 diabetes diagnosed before the age of 40 years had a 2–4 times higher risk of cardiovascular and non-cardiovascular mortality, heart failure, and ischaemic heart disease than did control populations. All of these risks were attenuated progressively with increasing age and substantially in individuals diagnosed after the age of 80 years.[57] Data from the National Diabetes Services Scheme between 1997 and 2011 involving 743 709 Australians with type 2 diabetes, showed that a diagnosis made 10 years earlier (equivalent to 10 years' longer duration of diabetes), was associated with a 20–30% increased risk of all-cause death and an approximate 60% increased risk of death due to cardiovascular disease.[58] In the Hong Kong Diabetes Surveillance Database including 770 778 patients with type 2 diabetes, all-cause and cause-specific death rates decreased by 50–80% between 2001 and 2016. However, in the age group of 20–44 years, death rates did not decrease with the standard mortality ratio fluctuating between 4·92 and 7·89 during the same period.[59]

Diagnosing, classifying, and managing young-onset diabetes and other diabetes subtypes

In the early 1980s, over 90% of European patients with diabetes who were diagnosed before the age of 30 years were considered to have classical type 1 diabetes due to autoimmune islet destruction with acute ketosis and absolute insulin deficiency.[60] In HICs, the tendency to develop ketosis means that patients with type 1 diabetes are less likely to default the medical system for too long before they present with acute emergencies.[61] However, in non-white populations, including those from Mexico,[62] India,[63] and China,[64] classical type 1 diabetes prone to ketosis is relatively uncommon in young adults diagnosed with diabetes. One study showed that in 2323 Chinese patients with young-onset diabetes, only 209 (9·0%) had classical type 1 diabetes.[61] In the remaining patients, 1478 (63·6%) were overweight and 636 (27·4%) had a healthy weight. After 9 years of follow-up, patients who were overweight with young-onset diabetes had a hazard ratio of 15·3 (95% CI 2·1–112·4) for cardiovascular disease and of 5·4 (1·8–15·9) for end-stage kidney disease. By contrast, patients with type 1 diabetes had the lowest event rates.

In the TODAY study and SEARCH study in the USA, adolescent-onset type 2 diabetes was characterised by rapid deterioration of β-cell function and poor metabolic milieu, compared with type 1 diabetes or late-onset type 2 diabetes.[65] In the TODAY study, metformin monotherapy was not effective (HbA_{1c} >7·9% [63 mmol/mol] for at least 6 months) in 120 patients (52%) with youth-onset diabetes (aged 10–17 years) during a 4 year follow-up period.[66] Hormonal perturbations during puberty might have contributed to increased insulin resistance and poor glycaemic control.[67] In the SEARCH study, researchers reported high blood pressure in 13 (31%) and high LDL

See **Online** for appendix

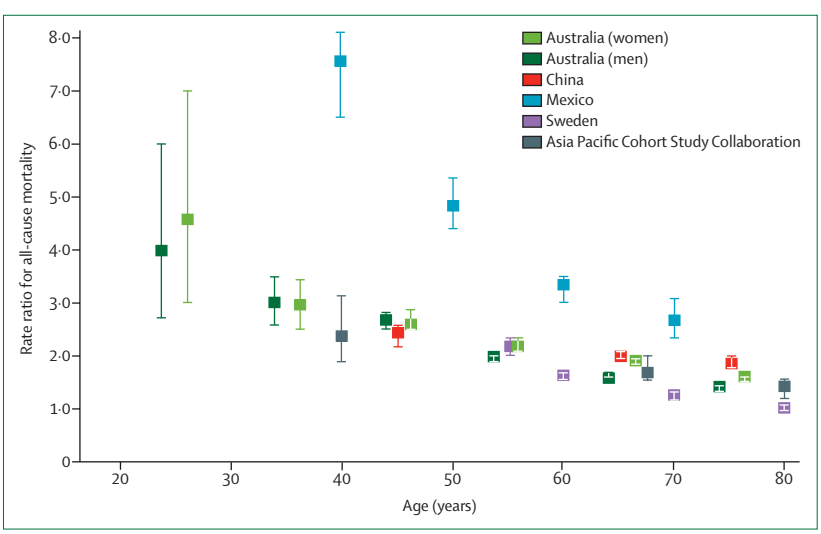

Figure 2: **Standardised rate ratio for all-cause mortality for people with diabetes compared with the general population, according to age and country**
Error bars show 95% CI. For the full references in this figure, see the appendix p 16.

cholesterol concentration in 16 (45%) of the non-Hispanic, white, young patients (aged 10–14 years) with type 2 diabetes.[68] In a position statement by the American Diabetes Association, maternal history of diabetes or maternal hyperglycaemia during the child's gestation, family history of type 2 diabetes, non-white ethnicity, features of insulin resistance (eg, polycystic ovary syndrome), and being small for gestational age are considered major risk factors for youth-onset diabetes,[69] with the combination of stunted early growth and adolescent obesity being a particularly strong risk factor.[70] Unlike patients with type 1 diabetes and adolescent-onset type 2 diabetes who are often managed in specialist centres by paediatricians, young adults diagnosed with type 2 diabetes aged between 18 years and 40 years are usually managed in primary care and adult specialist clinics. According to the US National Health and Nutrition Examination Survey, young adults (aged 18–44 years) were less likely to attain composite HbA_{1c}, blood pressure, and LDL cholesterol targets than were older adults (45–64 years), and the rates of target attainment did not improve during the 11 year observation period (ie, 2005–08 and 2013–16).[71] In Asia, despite considerable variations in the attainment of treatment targets across countries (probably reflecting varying quality of health-care systems), patients with young-onset diabetes had consistently worse control of risk factors than did patients with late-onset diabetes.[54]

Obesity and family history are prominent features in young-onset diabetes.[72] Despite not having classical type 1 diabetes presentation, patients with young-onset diabetes often require earlier insulin treatment than do individuals with late-onset disease.[73] In an analysis of Chinese patients from the Hong Kong Diabetes Register with young-onset diabetes, 122 (8%) of 1504 patients had glutamic acid decarboxylase antibodies suggestive of latent autoimmune diabetes in adults.[74] Although these patients had 60% lower risk of developing cardiovascular disease, they had a greater response to insulin than did patients without these antibodies (2·3% *vs* 0·7% reduction in HbA_{1c}), albeit with 60% higher risk of developing severe hypoglycaemia. Compared with patients with classical type 1 diabetes presentation, patients with young-onset diabetes who were positive for glutamic acid decarboxylase antibodies had an almost 3 times higher risk of end-stage kidney disease.[74] The discovery of common and rare genetic variants due to a single gene mutation with high penetrance, including maturity-onset diabetes of the young, calls for more precise diagnosis in young patients. Apart from family screening, identification of these genetic causes has implications for treatment selection, with some individuals benefiting from early insulin treatment and others from oral drugs.[75] Adding to this complexity, patients with young-onset diabetes often have multiple cardiometabolic risk factors, worsened by psychosocial distress,[40,76] with poor treatment adherence and frequent defaults from follow-up.[54,77,78] In a prospective population-based analysis, modelling showed that by delaying the onset of diabetes or by optimising control of all cardiometabolic risk factors, hospitalisation rates in patients with young-onset diabetes could be reduced by 30–60%.[42] However, the scarcity of evidence-based guidelines due to exclusion of young patients from large randomised controlled trials[79] poses additional challenges in optimising care for this patient group. Given their heterogeneous causes, long disease duration, and extremely high lifetime risk for life-threatening complications,[61,80] adults with young-onset diabetes, similar to type 1 diabetes, will benefit from interdisciplinary care in specialist-led diabetes centres for the ascertainment of causes (where possible) and from intensive risk factor management, including lifestyle intervention and psychosocial support as and when needed.

Phenotypic heterogeneity and variable treatment responses are not limited to patients with young-onset diabetes. In the UK Prospective Diabetes Study (UKPDS) of 3672 patients with type 2 diabetes, 361 patients (10%) had glutamic acid decarboxylase antibodies, 213 patients (6%) had islet cell antibodies, and 144 patients (4%) had both antibodies. These adults with latent autoimmune diabetes had the most rapid rate of oral medication failure and insulin requirement, especially among patients aged younger than 45 years.[81] In a multicentre Scandinavian cohort of 8000 adults with type 2 diabetes, researchers used glutamic acid decarboxylase antibodies; homoeostasis model assessment indices for β-cell function and insulin resistance, derived from fasting plasma glucose concentration and C-peptide values; HbA_{1c}; BMI; age of diagnosis; and age to classify patients into five groups with varying patterns of insulin insufficiency, autoimmunity, and insulin resistance that predict insulin requirement and chronic kidney disease.[82,83] With data from randomised controlled trials, other researchers supported the prognostic value of these clusters, but indicated that use of specific phenotypes, notably HbA_{1c}, age of diagnosis, estimated glomerular filtration rate, and blood pressure, outperformed these clusters in predicting treatment responses.[84] Taken together, these findings point to the increasing need to use data effectively to stratify risk and classify patients to personalise care, especially in young patients and individuals with an atypical presentation of diabetes.

Abnormal β-cell biology is a key feature of type 1 and type 2 diabetes

Glucose is an energy substrate essential for survival. In people with diabetes, there is insufficient insulin action (quantitative and qualitative) to utilise and store glucose effectively to maintain blood glucose concentration within a narrow range of 4–8 mmol/L at all times. The subsequent hyperglycaemia can lead to widespread protein glycation, inflammation, and oxidative stress with deleterious effects on organ structures and

functions.[85] Although autoimmune destruction of islets is considered the primary event in type 1 diabetes,[86] abnormal β-cell biology also has an important role in type 2 diabetes. In humans, considerable variations exist between individuals in the weight (0·5–1·2 g) and number of islets (100 000 to 2·3 million),[87] and BMI closely correlates with islet mass,[88,89] which is particularly relevant for people with diabetes living in low-income and middle-income regions, such as Africa.

Compared with individuals with normal glucose tolerance, people with impaired glucose tolerance have reduced first-phase insulin secretion with compensatory hyperinsulinaemia to correct hyperglycaemia, as well as non-suppression of glucagon levels during oral glucose ingestion.[90–92] To date, over 400 genomic loci have been found to associate with type 2 diabetes, with most of them implicated in islet biology, inflammation, adipogenesis, and cell cycles. Some of these loci are shared by other diseases, such as breast cancer, atrial fibrillation, and ischaemic heart disease, which might reflect the overlapping nature of these biological pathways with the frequent co-occurrence of obesity, diabetes, and other NCDs.[93]

Obesity, maternal hyperglycaemia, and perinatal development

In 2014, obesity affected 640 million adults and 110 million children and adolescents globally (10·8% of men, 14·9% of women, and 5·0% of children).[94] The prevalence of obesity has doubled over the past three decades, which is mirrored by a similar rising prevalence of diabetes in many parts of the world.[6] Childhood obesity can track into early adulthood and predict ischaemic heart disease in adulthood.[95] The rapid rise in childhood and adolescent obesity might contribute towards the rising trend of young-onset diabetes and premature development of other NCDs, if remedial actions are not taken.[54,96] In a large cohort of 62 565 Danish men, childhood overweight at 7 years of age was associated with increased risk of diabetes in adulthood, but only if it continued until puberty or beyond.[97] In the Swedish National Diabetes Register, independent of their country of origin, people with the earliest onset of diabetes (aged 18–44 years) had a higher BMI, worse cardiometabolic risk factors, and a more rapid deterioration in glycaemic control than did individuals with late-onset diabetes.[98]

Epidemiological evidence supports the presence of intergenerational transmission of diabetes and associated risk factors. In the Pima Indian population, the risk of developing diabetes was highest in the offspring of women with diabetes at conception (45·0% prevalence of diabetes in offspring), followed by the offspring of women who developed diabetes after pregnancy (8·6% prevalence), then by the offspring of women who did not have diabetes (1·4% prevalence). Because no increased risk of diabetes in offspring was related to paternal diabetes, these findings highlight the potential contribution of the intrauterine environment beyond genetic effects.[99]

Data from HAPO follow-up studies showed that the offspring of mothers with untreated gestational diabetes had an increased risk of obesity and diabetes at 7 years of age, independent of maternal BMI,[100] and increased adiposity at 10–14 years of age.[101] In the SEARCH study, participants had a high frequency of parental diabetes and type 2 diabetes was diagnosed 1·68 years earlier among individuals exposed to diabetes in utero than among individuals whose mothers' diabetes was diagnosed later, after adjusting for age of diagnosis of maternal hyperglycaemia, paternal diabetes, sex, and race or ethnicity.[101] By contrast, paternal diabetes was not associated with age of onset of diabetes.[102] In the SEARCH study, it was estimated that 47·2% (95% CI 30·9–63·5) of youth-onset type 2 diabetes was attributable to maternal diabetes or maternal obesity.[103] Various combinations of high and low birthweight, and childhood obesity can result in an early age of diagnosis of diabetes. Premature puberty and pregnancy in the daughters of mothers with a history of gestational diabetes might repeat the same pattern of maternal obesity and hyperglycaemia, leading to intergenerational transmission of diabetes (figure 3).[104]

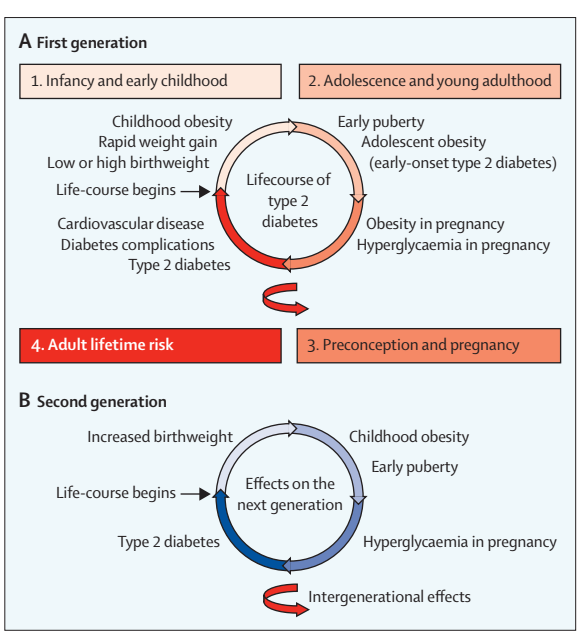

***Figure 3*: The role of different risk factors at various life-course stages in the development of type 2 diabetes**

The life-course of type 2 diabetes in the first (A) and second generation (B). Adolescent obesity and maternal hyperglycaemia contribute to the risk of type 2 diabetes in the next generation, and perpetuate the rising prevalence of young-onset diabetes. Numerous opportunities exist for the prevention and intervention of diabetes during the life-course. Red arrows indicate a combination of different effects on the following generation, including maternal hyperglycaemia and obesity (by directly modulating growth and epigenetic mechanisms), altered microbiome, shared genetics and behaviour, and environmental exposures. Reproduced from Ma and Popkin,[104] by permission of Public Library of Science.

Apart from shared environment, socioeconomic position, and lifestyle, the unfavourable metabolic milieu starting from pregnancy and other external factors throughout a life-course can affect gene expression (ie, epigenetics) to influence multiple pathways manifested as various phenotypes (eg, obesity, inflammation, and β-cell dysfunction) to perpetuate the adverse consequences of diabetes and its complications. Globally, hyperglycaemia occurs in 17% of pregnancies, making the contribution of this intergenerational transmission of type 2 diabetes substantial.[104,105] Women with maternal obesity and hyperglycaemia are at high risk of developing type 2 diabetes and cardiovascular disease. Pregnancy is a great opportunity to influence the future health of mother and child. Integrating maternal and child health care, including perinatal education, postnatal assessment, and advice on individual maternal risks for diabetes, can be the first step towards this important goal.[106] However, only about 30% of women attend postnatal glucose testing, calling for implementation of local strategies to reach most women. User friendly screening tests (eg, risk scores, fasting blood glucose concentration, and HbA_{1c}) can be used to increase the postnatal testing rates in these women at high risk.[107] Taken together, the high prevalence of maternal hyperglycaemia and its potential effects on future generations suggest the importance of public health action at early stages in the life-course. By producing results that go beyond generations, this action has far-reaching impact.[108]

Use of the term epidemic to describe diabetes: the importance of environment and behaviour

The word epidemic is often used to describe the global challenge of diabetes. This term refers to the increase of a disease above the expected level in a particular setting. In its classical definition, the occurrence of an epidemic, such as cholera, requires the presence of an environment (eg, poor sanitation), an agent (eg, bacteria), and transmission to a susceptible individual (eg, host).[109] Diabetes is a classic example of a complex disease because it has multiple causes, none of which are either necessary or sufficient for disease development.[110] However, changes in the ecosystem and human behaviour, which are prominent features in the current epidemics of diabetes and other NCDs, can be viewed as complex events because of the environment–host interactions, which require a sociobiological strategy.

Ethnicity, socioeconomical development, and risk of diabetes and its complications

Non-white populations (notably Mexicans, Africans, and east Asians) only need a small increase in adiposity to develop diabetes, partly due to insufficient insulin response to compensate for insulin resistance associated with weight gain.[91,111] In the US Multiethnic Cohort, the age-adjusted prevalence of diabetes ranged from 6·3% in white populations to 10·2% in Japanese, 16·1% in native Hawaiians, 15·0% in African Americans, and 15·8% in Latinxs. After adjustment for other risk factors, the 2 times higher risk for diabetes among non-white populations remained in all BMI categories.[112] The marked increase in diabetes prevalence in migrants living in societies characterised by lifestyle and environmental factors that increase diabetes risk and who originate from LMICs, as well as the exponential rise in diabetes prevalence in LMICs with socioeconomic development, highlight the importance of environment–host interactions.[113]

On an individual level, diabetes risk can be further influenced by age, sex, ethnicity, genetics, and educational level. The effects of rural–urban migration are apparent in many countries experiencing economic development. For example, in a nationally representative, population-based survey of 1·3 million adults in India between 2012 and 2014, the crude prevalence of diabetes varied from 3·2% to 19·9% and that of hypertension ranged from 18·0% to 41·6%, with variations in age, state, and rural versus urban locations.[114] In another prospective epidemiological survey of 9848 adults in India between 2006 and 2016, the most rapid increase in diabetes prevalence occurred in towns (from 16·4% to 20·3%) and periurban villages (from 9·2% to 13·4%) compared with cities (from 18·6% to 21·9%), in which age, family history of diabetes, and central obesity were major risk factors.[115]

Given the cross-influence between ecological and biological development, in the early 1990s, anthropologists warned against the potential mismatching between biology and changes in lifestyle and risk factors associated with industrialisation and economic growth, leading to "diabetes running wild".[116] The tendency of Asian, Africans, and Latinxs to store fat centrally rather than peripherally contributes to the early development of insulin resistance. Despite the generally low BMIs of individuals in these populations, this preponderance for visceral fat deposition is often associated with increased lipolysis and inflammatory responses.[117] Many theories have been suggested to explain the global epidemic of diabetes. In the so-called capacity–load model, an imbalance between metabolic load (eg, obesity, sedentary behaviour, diets high in sugar or fat, psychosocial stress, smoking, and responses to infection) and metabolic capacity can lead to abnormal physiological traits and an inability to maintain metabolic homoeostasis and vascular health. This metabolic capacity is largely framed by maternal health and early life development, which can be further influenced by environmental factors. These factors might be particularly relevant in LMICs.[118]

Other researchers have hypothesised that genetic traits, phenotypes, or a combination of both, which promote efficient energy storage and activation of the stress and inflammatory responses, might confer survival advantages in an environment that is deprived of food, physically strenuous, and rich in pathogens.[119] Thus, people with ancestors who led a subsistent lifestyle

might have a phenotype of low BMI closely correlated with β-cell mass,[89] and strenuous physical activity and external stressors (eg, infections) might encourage storage of visceral fat for efficient release of free fatty acids and cytokines. These combined traits of insulin resistance and relative insulin insufficiency might be particularly relevant in populations that undergo rapid nutritional and lifestyle transitions.[64,120,121] To this end, increased activity of the sympathetic nervous system, hypothalamus–pituitary–adrenal axis, renin–angiotensin system, and innate immunological responses have been reported in patients with type 2 diabetes. Together with ageing, characterised by reduced secretion of growth hormone, IGF-1, and sex steroids, which can collectively lead to reduced lean body mass and increased adiposity, multiple subphenotypes (including obesity, metabolic syndrome, cardiovascular–renal dysfunction, and possibly cancer) might emerge, all of which share common biological pathways.[64,122,123]

Changing demographics, environment, and ecosystem

The demographic ageing transition,[6] along with increasing obesity[94] and physical inactivity,[124] are driving the global diabetes epidemic. Globalisation has transformed our ecosystem and many aspects of daily life. The flow of information through different media and ease of transportation have promoted cultural exchanges among different countries and regions. The increased production of goods and free trade agreements have led to changes in leisure and non-leisure activity; excessive screen time; qualitative changes in diet, favouring sugar-sweetened beverages and sodium, and reducing intake of grains, fruits, and vegetables; increased portion sizes; and change in work schedules, which all in turn alter dietary patterns and sleep schedules. In LMICs, food insecurity, poor affordability of healthy foods (eg, fresh fruits, vegetables, whole grains), undernutrition, and high consumption of low-quality calories are not uncommon, and are often made worse by poverty.[113,125] Similarly, in HICs, underserved communities often have few choices in leisure activities, are likely to consume more energy-dense food, and often cannot afford healthy foods that tend to be expensive.[126,127] In the latest GBD 2017 analysis, dietary factors explained as much as 20% of the attributable risk of NCD.[128]

Environmental pollutants, many of which are endocrine disruptors (eg, bisphenol A), have also been implicated in causing diabetes, obesity, and cardiovascular–renal diseases.[129,130] These environmental factors might be particularly relevant in LMICs where the prevalence of obesity is lower than that in HICs.[131] Other reports have highlighted the effects of extreme temperatures in increasing the risk of cardiovascular events in people with diabetes.[132] Social problems arising from rapid rural–urban migration such as overcrowding, social isolation or disparity, and psychosocial stress might contribute to the multidimensional nature of diabetes. These risk factors can be worsened by poor hygiene, chronic low-grade infections (notably viral hepatitis B and C), and industrial pollution. Although these factors might theoretically contribute to the development of diabetes, more research is needed to quantify the effects of these societal changes on health and disease including, but not limited to, diabetes and other NCDs in different populations living across various environments.[15]

Multimorbidity of diabetes in LMICs and underserved communities

The interactions between chronic infections (notably tuberculosis) and NCDs (eg, diabetes) are particularly relevant to low-income and middle-income regions such as India, Africa, and Mexico, which are hit by these double burdens.[133] Together with the emerging evidence on the damaging effects of severe acute respiratory syndrome coronavirus 2 on pancreatic islets, there is a possibility that the diabetes epidemic will worsen against the backdrop of the COVID-19 pandemic.[134] These two public health emergencies are likely to hit LMICs and underserved communities in HICs the hardest. The multimorbidity of diabetes in subpopulations and communities within a socioeconomic and cultural context highlights the considerable heterogeneity of disease predisposition, clinical patterns, and social and medical needs, which will require a multidimensional strategy.[116]

Aside from infections, researchers have reported independent associations of obesity, diabetes, and cardiovascular disease with low levels of educational attainment and socioeconomic position, which contribute to unhealthy lifestyles.[135,136] In a population-based cohort in Scotland, life expectancy in people with type 2 diabetes was reduced at all ages and levels of socioeconomic position, with a loss of 5·5 years in women aged 40–44 years in the second most deprived quintile of socioeconomic position.[137] In the USA, mortality related to diabetes is closely associated with low-income status, low levels of educational attainment, and non-European ethnicity.[138] Within workforces, long working hours, poor sleep hygiene, and shift work were associated with an increased risk of obesity and diabetes.[139,140] Low levels of educational attainment might interact with high personal income to increase the risk of diabetes in populations whose affluence has changed in recent years.[141] In LMICs, rural–urban migration and social mobilisation might be accompanied by other stressors that can lead to risk-conferring behaviours, such as the use of tobacco and binge drinking. In China, high income and high levels of educational attainment were associated with an increased risk of diabetes in men; whereas, in women, high levels of educational attainment were associated with a reduced risk of diabetes, with income having little or no effect size.[142]

The clustering of these risk factors is further modified by socioanthropological factors, such as geophysical

environment, familial socioeconomic position, age of migration, levels of acculturation, and adaptation to new cultures. The social gradient of diabetes in LMICs can be complex. Such gradient depends on the specific measure of socioeconomic position and the level, speed, and pattern of economic development. The gradient might be positive in some countries and negative in others for some measures of socioeconomic position,[143–145] where low socioeconomic position might be associated with a lifestyle of increased physical activity and decreased access to excess dietary calories. The frequent clustering of diabetes, depression, and poverty in LMICs and in underserved and new migrant communities in HICs highlight the synergistic problems that affect the health of a population within the context of persistent social and economic inequalities (sometimes referred to as a syndemic).[146,147] The impact of COVID-19, with high rates of death among not only individuals with diabetes but also people from particular communities (eg, African Americans and minor ethnicities) where inequalities, poor access to care, and comorbidities often prevail, is a wake-up call regarding the need to protect vulnerable populations.[148]

To this end, the 2019 *Lancet* Commissions[149,150] on the close links between climate change, food systems, and global epidemics of obesity and NCDs remind us once again of the fragility of human health in a rapidly changing ecosystem,[151–153] which calls for an integrated sociobiomedical approach to protect health and prevent disease (figure 4). In recognition of these societal determinants of NCDs, environmental protection and mental illness have been included as top agenda items in the fight against NCDs in the 2019 General Assembly of the UN.[154]

The health-care and societal costs of diabetes

The disproportionately higher rate of increase in health-care expenditure than that in gross domestic product (GDP) is partly due to ageing, rising costs of technology, and increasing expectations from patients and the public. This discrepancy between earning and spending calls for improvements in health-care planning and in the cost-effective use of finite resources.[155] In 2016, global spending on health care was US$10·3 trillion (adjusted for purchasing power) in total, or $1400 per capita.[156] The respective per capita spending on health care has increased at an annual rate of 4·0% from 1995 to 2016. This spending is expected to continue increasing to $2373 per capita by 2050, at a rate that exceeds the growth of national income.[157]

In 2010, around a tenth of global health-care expenditure was devoted to the treatment of diabetes, mainly for treatment of its complications and comorbidities.[158] In 2017, the cost of health care for people with diabetes accounted for a quarter of health-care expenditure in the USA, equivalent to an average of $16750 per person, which is 2·3 times higher than health-care costs for an individual without diabetes.[159] In the USA, with predominantly private health care, individuals with diabetes and ischaemic heart disease, congestive heart failure, hemiplegia, and amputation had 50–70% higher costs than did patients with diabetes without complications.[160] Furthermore, patients with end-stage kidney disease who had received a renal transplant had 500% higher costs.[160] In a report from Italy, where health care is largely publicly funded, researchers used a simulation model and estimated that the average annual cost per patient with diabetes could rise from $382 in individuals without morbidities

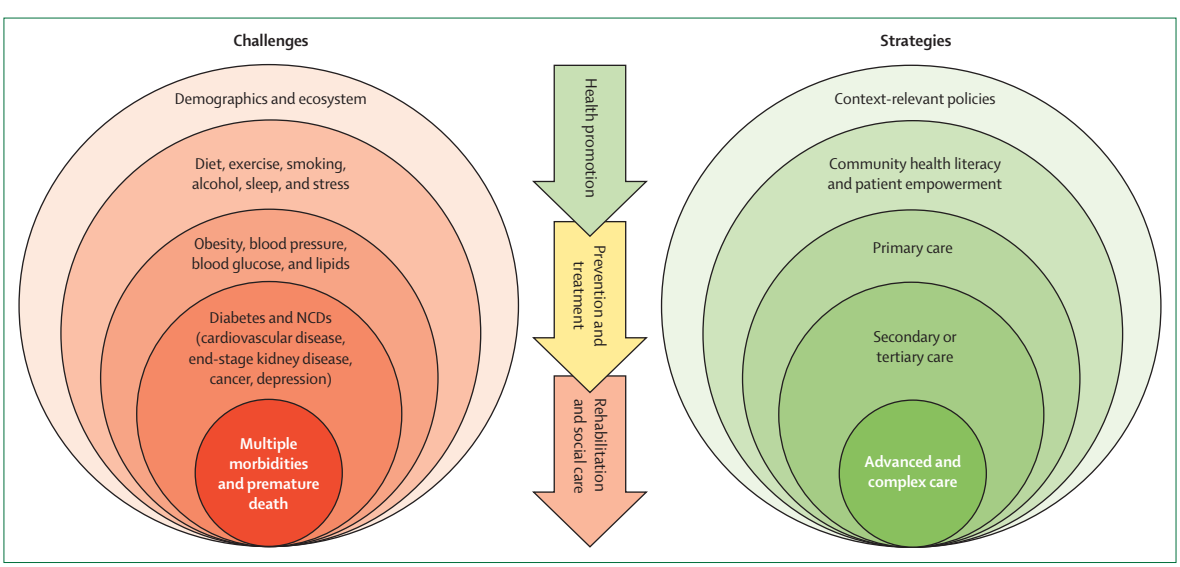

Figure 4: **Challenges and strategies for health promotion, disease prevention, treatment, rehabilitation, and social care in diabetes and NCDs**
The challenges of complex environment–lifestyle–host interactions underlying diabetes and NCDs require a combination of personal and societal strategies by use of context-relevant policies and system change to cover the full spectrum of health promotion, prevention, treatment, rehabilitation, and social care (see table 3; panel 4; figure 11). NCD=non-communicable disease.

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to $7937 in patients with coronary, cerebrovascular, renal, and retinal complications.[161] Irrespective of the number of comorbidities, over 70% of the costs were due to hospitalisation. Two-thirds of direct health-care expenditure was due to treatment of complications, with outpatient care and medications accounting for a small proportion of total costs.

Apart from direct medical costs, which include outpatient and inpatient services, emergency care, medications, laboratory tests, medical equipment and supplies, and long-term care, people with diabetes might have reduced work performance. This patient group might also have an increased number of days missed at work because of their health condition, and their working lives might be cut short by permanent disability and premature death.[162] The productivity loss due to reduced working lives, sick leave (ie, absenteeism), and reduced work performance (ie, presenteeism) are indirect costs of diabetes. If a large population of young individuals are affected by diabetes, their productive potential will be reduced, resulting in reduced growth of national economies. The loss of earnings can lead to a vicious cycle whereby diabetes aggravates poverty, which can worsen access to care, lead to poor outcomes, and result in low productivity.

People in LMICs and, to some extent, individuals and their families from underserved communities in HICs often have low levels of awareness of diabetes and financial difficulty to pay for their diabetes care, even for basic medications and consultations aimed at preventing hospitalisations and occurrence of devastating illness (table 1). In 2010, although 70% of individuals with diabetes lived in LMICs, more than 90% of global expenditure on diabetes care was in HICs. Health-care expenditure on diabetes also varies greatly, ranging from 2% in Rwanda to 41% in Nauru of a country's total health-care expenditure.[158] Compared with the decreasing prevalence of cardiovascular disease in North America and Europe, the 2–3 times higher (and increasing) incidence of cardiovascular disease and mortality from diabetes in LMICs (eg, India[163]) suggests the need to increase investment in preventive care in these settings, which can least afford to pay for expensive treatment for late complications.

In 2015, the estimated global indirect cost of diabetes was US$294 billion, or 35% of the total economic burden of diabetes. Of the total indirect cost, 94% was due to either premature death or drop out from employment because of disability. The indirect cost from premature death was over 64% in LMICs and 60% in HICs. Individuals with diabetes in LMICs tend to die at a younger and more productive age than do people with diabetes in HICs.[164] The global economic burden of diabetes is expected to increase due to the growing population of people with diabetes and the increase in medical expenditure for diabetes per capita. The projected total global economic cost due to diabetes is predicted to increase from $1·3 trillion (1·8% of global GDP) in 2015 to $2·2 trillion (2·2% of global GDP) in 2030.[165] Under these projections, the direct global medical cost would increase from $0·86 trillion to $1·70 trillion, and the indirect global cost would increase from $0·46 trillion to $0·78 trillion.[165]

From an economic perspective, the substantial amount of resources used to treat diabetes and its complications could be used for other productive activities, including prevention measures.[166] Some studies have simulated the impact of diabetes on GDP at a country or global level. Predictions have shown that global GDP might have been $1·7 trillion higher between 2011 and 2030, if diabetes had been eliminated in 2010. Although such losses would be borne largely by HICs (53% of total GDP), the predicted GDP loss was $49 billion for China and $15 billion for India.[164] Another study estimated that

For more on **this consumer price index** see https://www.bls.gov/cpi/data.htm

	Total annual out-of-pocket cost for care related to diabetes per person		Out-of-pocket cost as proportion of total health-care cost related to diabetes (%)	Out-of-pocket cost as proportion of personal or family income (%)
	Original estimates, US$ (year)	Estimates for 2017, US$*		
Low-income and middle-income countries				
India				
Type 1 diabetes	455 (2012)	521	87%	16%
Not specified	515–526 (2009)	652–665	98–100%	NA
China				
Type 2 diabetes	596 (2013)	666	NA	6% for high-income households; 32% for low-income households
Pakistan				
Type 2 diabetes	197 (2006)	278	100%	18% for low-income households
Sudan				
Type 1 diabetes	280 (2004)	429	99%	23%
Nigeria				
Type 2 diabetes	1558 (2013)†	1742	100%	NA
High-income countries				
USA				
Not specified	Privately insured: 1184 (2013)	1324	Privately insured: 11%	NA
Not specified	Medicaid: 260 (2008); uninsured: 1119 (2008)	Medicaid: 339; uninsured: 1461	Medicaid: 3%; uninsured: 40%	NA
Type 1 diabetes	Medicare: 542 (2013)	606	NA	NA
Type 2 diabetes	Medicare: 529 (2013)	591	NA	NA
Canada				
Type 1 diabetes	808–3693 (2015)	860–3930	22–81%	3–17%
Type 2 diabetes	544–1440 (2015)	579–1532	36–70%	2–9%

For the full references in this table, see the appendix p 13. NA=not applicable. *Adjusted to US$ estimates from 2017 with the medical care part of consumer price index. †Recalculated by excluding non-medical cost (eg, transportation and diabetes diet) from original estimates.

Table 1: **Out-of-pocket cost for people with diabetes in selected countries (US$ per person per year)**

Finland's GDP would be 1·1% higher, if diabetes were eliminated.[167]

Access to care, education, and medications in type 1 diabetes

In HICs, the major current focus in type 1 diabetes is on reducing the treatment gap in the prevention of microvascular or macrovascular complications as the leading cause of death.[168] The situation is far worse in LMICs, where poverty and insufficient infrastructure and professional knowledge often lead to scarce insulin availability and poor access to education on diabetes. As a result, children with type 1 diabetes in these settings often have an extremely poor outlook, are frequently misdiagnosed, develop acute and chronic complications, and die prematurely.[169–171] Competition between manufacturers has led to the availability of relatively inexpensive insulin products, which should be made part of WHO's *Model Lists of Essential Medicines* and made affordable and available with appropriate use in all LMICs.[169,170,172,173]

Ensuring access to insulin and patient education to improve patient self-management

A particular concern for people with type 1 diabetes is the high level of training needed for not only physicians but also nurse educators, dietitians, and social workers. In turn, tailored education on diabetes for patients and relevant family members is important, covering not just insulin and self-monitoring of blood glucose concentration but also diet (preferably with carbohydrate counting), exercise, and other factors.[174] Attention needs to be given to the time at school for children, addressing stigma, managing sick days, and dealing with issues of adolescence (including contraception and pregnancy planning). Education materials should be culturally sensitive and written in an accessible way. The transition from adolescence to adulthood with use of adult health-care services is a pivotal period that needs locally adapted and effective programmes.[175] Monitoring and benchmarking efforts are key to achieving improved care, and international benchmarking efforts are available. Highlighting different outcomes between clinics in similar situations can provide the impetus for improving organisation and quality of care.[176,177]

Insulin analogues are now widely used in many countries. Basal insulin analogues are better than human or animal insulins (eg, bovine and porcine sources) for minimising the risk of nocturnal hypoglycaemia, and are particularly useful for basal–bolus regimens (ie, therapy involving multiple injections a day of long-acting or intermediate-acting insulin and short-acting or rapid-acting insulin at each meal).[178,179] Nevertheless, human and biosimilar insulins are more affordable insulins in LMICs than insulin analogues.[180,181] In patients with type 1 diabetes, basal–bolus insulin regimens offer better glycaemic control than twice daily regimens, if accompanied by the appropriate education of individuals with diabetes, family, and care providers with access to adequate supplies of needles, lancets, and testing strips for self-monitoring blood glucose concentration. However, the cost of self-monitoring is often higher than that of insulin.[182] In some LMICs, the tariffs on insulin and self-monitoring supplies often reduce the affordability of these treatments.

Many clinics still use insulin regimens twice a day, often with premixed insulin.[169] These regimens are usually associated with higher HbA_{1c} and more frequent hypoglycaemia than are basal–bolus insulin regimens, especially when used with little or no self-monitoring of blood glucose concentration and diabetes education.[183] However, other non-insulin determinants of quality of glycaemic control are also important.[183] In LMIC settings, due to limited insulin, food insecurity, the unavailability of devices to self-monitor blood glucose and emergency glucagon injection kits, and scarce transport and emergency services, there is a tendency to reduce the dose of premixed insulins to avoid hypoglycaemia. All of these factors can increase the risk of poor glycaemic control and complications that can adversely affect growth and quality of life.[175] Even in HICs, poverty, varying health-care financing or insurance policies, lack of price transparency, complexity in supply chains, and insufficient competition among a few manufacturers have made insulin and supplies to self-monitor blood glucose concentration difficult to afford.[184,185]

Use of diabetes centres to build capacity and to improve standard of care in type 1 diabetes

The global impact of type 1 diabetes can be diminished through widespread development of infrastructure and capacity in LMICs to improve patient care. Professional and patient education are prerequisites for good care. According to national and international guidelines, health-care providers must be taught how and when to measure blood glucose concentration in symptomatic children (to prevent death from misdiagnosis) and become habituated to doing so as a matter of routine.[171,175,183,186] The establishment of specialised diabetes centres or regional type 1 diabetes centres in LMICs provide a focal point for building capacity to improve management of acute emergencies and complex problems. Extra support might be needed for patients living in remote areas, due to increased travel and indirect costs. The spread of mobile phone technology in many LMICs provides an opportunity for 24 h emergency advice. Peer support also offers potentially profound advantages. Although models of care should be adapted to each country's available resources and health-care system, they should aim to provide at least an intermediate level of care as per the levels of care (table 2), either at no cost to patients, or at a cost affordable for every person with diabetes.[183]

In some countries, programmes such as the Life for a Child, Changing Diabetes in Children,[187] and Insulin for Life, with in-kind support from pharmaceutical

For more on **Life for a Child** see www.lfacinternational.org

For more on **Insulin for Life** see https://www.insulinforlife.org

	Insulin	Monitoring of blood glucose concentration	HbA_{1c}	Screening for complications	Diabetes education	Interclinic mean HbA_{1c} ranges	Mortality and complications
Minimal care							
1A	Human insulin, premixed insulin only, injections once to twice a day	Only at clinic	None	None or just weight	Minimal or no diabetes education; care from general physician or paediatrician	12·0–14·0% (108–130 mmol/mol)	High mortality from misdiagnosis and acute complications; serious early-onset complications common in survivors in the long term
1B	Human premixed insulin only, injections twice a day	One to two tests per day	Done in the laboratory or at the point of care	Weight, height, blood pressure, visual acuity, and light touch	Some diabetes education, care by adult diabetologist or paediatrician; education about insulin dose adjustments	9·5–12·0% (80–108 mmol/mol)	Substantial mortality; serious early-onset complications common in the long term
1C	Human insulin, short-acting and long-acting, injections twice a day	One to two tests per day	Done in the laboratory or at the point of care	Weight, height, blood pressure, visual acuity, and light touch	Some diabetes education, care by adult diabetologist or paediatrician; education about insulin dose adjustments	9·0–10·5% (75–91 mmol/mol)	Substantial mortality; serious early-onset complications common in the long term
Intermediate care							
2A	Human insulin, multiple injections a day (basal–bolus regimen)	Two to three tests per day	At point of care	Weight, height, blood pressure, eyes, feet, urinary albumin, creatinine, lipids; treatment as indicated; access to glucagon if possible	Diabetes education appropriate for stage; care by paediatric or adult endocrinologist and nurse educator, with dietitian and social worker if possible; diabetes camps; peer and school support; 24 h emergency call service	8·0–9·5% (64–80 mmol/mol)	Infrequent mortality; serious complications in the long term rare, unless control of blood glucose concentration is suboptimal
2B	Human insulin, multiple injections a day, with or without insulin pens	Four or more tests per day	At point of care	Weight, height, blood pressure, eyes, feet, urinary albumin, creatinine, lipids; treatment as indicated; access to glucagon if possible	Diabetes education appropriate for stage; care by paediatric or adult endocrinologist and nurse educator, with dietitian and social worker if possible; diabetes camps; peer and school support; 24 h emergency call service	8·0–9·5% (64–80 mmol/mol)	Infrequent mortality; serious complications in the long term rare, unless control of blood glucose concentration is suboptimal
Comprehensive care							
3A	Insulin analogues (basal–bolus regimen) with insulin pens	Five or more tests per day	At point of care	Full screening for complications and fundus photography, thyroid, coeliac monitoring (at frequency according to guidelines); treatment as indicated; access to glucagon	Diabetes education appropriate for stage; multidisciplinary team with paediatric diabetologist, nurse educator, dietitian, social worker, and psychologist; diabetes camps; peer and school support; 24 h emergency call service	6·5–8·5% (48–69 mmol/mol)	Mortality rare; complications in the long term delayed or prevented entirely, except if blood glucose control is suboptimal
3B	Insulin pump with consumables	Five or more tests per day	At point of care	Full screening for complications and fundus photography, thyroid, coeliac monitoring (at frequency according to guidelines); treatment as indicated; access to glucagon	Diabetes education appropriate for stage; multidisciplinary team with paediatric diabetologist, nurse educator, dietitian, social worker, and psychologist; diabetes camps; peer and school support; 24 h emergency call service	6·5–8·5% (48–69 mmol/mol)	Mortality rare; complications in the long term delayed or prevented entirely, except if control of blood glucose concentration is suboptimal
3C	Insulin pump with consumables	Continuous monitoring with consumables	At point of care	Full screening for complications and fundus photography, thyroid, coeliac monitoring (at frequency according to guidelines); treatment as indicated; access to glucagon	Diabetes education appropriate for stage; multidisciplinary team with paediatric diabetologist, nurse educator, dietitian, social worker, and psychologist; diabetes camps; peer and school support; 24 h emergency call service	6·5–8·5% (48–69 mmol/mol)	Mortality rare; complications in the long term delayed or prevented entirely, except if control of blood glucose concentration is suboptimal
3D	Artificial pancreas with consumables	Continuous monitoring with consumables	At point of care	Full screening for complications and fundus photography, thyroid, coeliac monitoring (at frequency according to guidelines); treatment as indicated; access to glucagon	Diabetes education appropriate for stage; multidisciplinary team with paediatric diabetologist, nurse educator, dietitian, social worker, and psychologist; diabetes camps; peer and school support; 24 h emergency call service	6·5–8·5% (48–69 mmol/mol)	Mortality rare; complications in the long term delayed or prevented entirely, except if control of blood glucose concentration is suboptimal

Adapted with permission from the Life for a Child Programme by Ogle and colleagues.[183] Levels of care are ordered from lowest priority to highest priority. HbA_{1c}=glycated haemoglobin A_{1c}.

Table 2: **Levels of care in children and young adults with type 1 diabetes**

industries and expert volunteers, have substantially improved care and outcomes.[170] Education resources for patients and families, such as videos, graphic novels, and so-called conversation maps (ie, an innovative group education tool guided by a facilitator that uses maps to help patients to come to terms with living with diabetes) simplify treatment guidelines. Two African training colleges for paediatric endocrinologists are also now available. However, many of these programmes are supported by one-off philanthropic donations. Improvements to health systems within countries could provide a sustainable support system that could have long-term benefits on the health outcomes of children with type 1 diabetes.

Type 1 diabetes registers show a secular improvement, but with major care gaps

For more on the **International Diabetes Federation** see https://www.diabetesatlas.org

Although many registers of childhood-onset type 1 diabetes exist, documentation of the overall burden arising from this type of diabetes is incomplete. There are two main deficiencies. First, incidence and prevalence data from many parts of the world, notably sub-Saharan Africa, are scarce. Second, few studies have focused on adult-onset type 1 diabetes. The incidence of childhood-onset (aged <15 years) type 1 diabetes was extensively reported in the landmark DIAMOND study, initiated by WHO in 1990. The report included data from 112 registers in 57 countries and suggested a 400 times variation in annual incidence, ranging from less than 1 case per 100 000 people (in China and Venezuela) to 41 cases per 100 000 people (in Finland).[188] Some of this difference might be due to not recognising cases in resource-limited countries; however, differences in incidence of up to 30 times have also been observed among HICs (eg, between Finland and Japan).

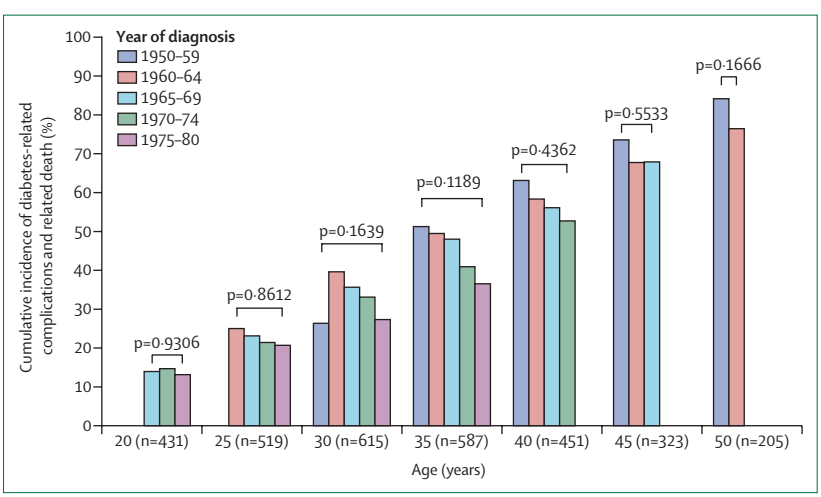

Figure 5: **Cumulative incidence of diabetes-related complications and death from the Pittsburgh Epidemiology of Diabetes Complications cohort**

Patients in this cohort had childhood-onset type 1 diabetes. p values were calculated via independent χ^2 tests comparing incidence between the two observation periods, and they highlight how these trends have not improved within each age group diagnosed during different time periods.

Nevertheless, this large study had little representation from sub-Saharan Africa and did not address prevalence, an indicator of disease burden. Based on the available data, childhood incidence generally increased with age and peaked in individuals aged 10–14 years. There was a male preponderance in countries at high risk and a female preponderance in countries at low risk. In European countries, incidence of childhood-onset type 1 diabetes had risen by about 3% per year from 1989 to 2003,[189] although this rise now appears to be slowing in countries at high risk, such as Finland[190] and Norway.[191] Such a trend has also been seen among non-Hispanic white populations in the USA.[192] These trends compare with countries at low risk and among populations in China,[193] Korea,[194] and Hispanics in the USA,[192] where higher increases in incidence have been seen. Striking increases in the incidence of childhood-onset type 1 diabetes might also occur in low-income countries, partly due to increased case ascertainment as care improves.[171] In 2017, the International Diabetes Federation estimated that there were 1·1 million children and adolescents aged younger than 20 years with type 1 diabetes. Although the incidence of type 1 diabetes in adults was somewhat lower than that seen in adolescents, the few available studies in adults suggested that the condition continued to occur throughout adulthood. In Sweden, the incidence of type 1 diabetes fell from 37 cases per 100 000 people before 20 years of age to 27 cases per 100 000 people thereafter, and the rates for individuals aged 70–79 years were higher than for those for children aged younger than 9 years.[195] These findings underscore the importance of extensive data and studies of type 1 diabetes in adults, despite the difficulties in typology (ie, classification), which is a considerable barrier without extensive laboratory testing.

The burden of type 1 diabetes reflects not only its prevalence and management requirements but also the risk of major complications in the long term and their consequences (eg, visual loss, foot ulcers, cardiovascular disease, lower extremity amputation, diabetes-related death). According to data from the Pittsburgh EDC study,[196] after 30 years of exposure to hyperglycaemia, 80% of patients with type 1 diabetes suffered one or more of these complications (figure 5). Although the bar charts visually suggest decreasing incidence of complications across different cohorts, none of these trends were significant, indicating no improvement in these complication rates over time (figure 5). These data highlight the urgent need to further improve clinical management, particularly for hypertension, as reported in another EDC subanalysis.

In HICs such as Australia, the death rate of patients with type 1 diabetes is less than 2 per 1000 person-years. By contrast, reports from Africa and central Europe indicate that mortality rates are 9 or more times higher. In the USA, Europe, and areas that generate national data of high quality (eg, Taiwan), life expectancy of patients with type 1 diabetes has improved over time; however, an individual with this type of diabetes might

still lose up to 17 years of life compared with the general population.[197] To put this figure into perspective, patients diagnosed with type 1 diabetes in the USA in the early 1920s, soon after insulin therapy was developed, could expect to lose 30 years of life. Despite the marked improvement in survival in HICs, such improvements have not been seen in LMICs (figure 6).

Nevertheless, social disparity is a major barrier to care in HICs. Between 1979 and 1984, type 1 diabetes was associated with a loss of 30 years in life expectancy among African Americans in the USA, compared with a loss of 20 years in the general population.[198] Although survival rates improved in a 2010 analysis, the gap between African Americans and the general population has persisted.[168] In Scotland, from the period 2006–10 to the period 2011–15, the age-standardised mortality rate per 1000 person-years in people with type 1 diabetes decreased from 24·8 to 20·4 in men and from 22·5 to 17·6 in women. However, during the same time-frame, the rate ratios for the most deprived populations versus the least deprived populations increased from 2·49 to 2·81 in men and from 1·92 to 2·86 in women.[199] These marked variations in type 1 diabetes survival over time, between and within countries, highlight the effects of national socioeconomic development and social or care disparities on clinical outcomes, even in HICs.[200–202]

Standardised mortality ratio and excess deaths due to care gaps in young individuals with type 1 diabetes

In HICs, quality care (defined as guideline-based comprehensive care) is generally provided to young individuals with type 1 diabetes. By contrast, most young individuals in low-income and low-to-middle-income countries, and many young individuals in upper-middle-income countries, receive minimal or intermediate care (table 2).[183] We estimated the excess mortality due to this care gap in individuals aged younger than 25 years and diagnosed with type 1 diabetes before 20 years of age. We calculated this estimate by searching the scientific literature for mortality data in young individuals with this type of diabetes diagnosed during childhood or adolescence, wherein the standardised mortality ratio (SMR) was stated or could be calculated by comparing the stated mortality rate with background mortality by use of WHO's data on life tables. 18 studies were identified on comprehensive care from HICs, three on intermediate care from upper-middle-income countries, seven on intermediate care from lower-middle-income and low-income countries (pooled), and one on minimal care from lower-middle-income and another from low-income countries. A weighted (by person-years of follow-up) mean SMR was then calculated for HICs (comprehensive care; SMR 2·5), upper-middle-income countries (intermediate care; estimated SMR 4·9), lower-middle-income countries (50% minimal and 50% intermediate care; estimated SMR 13·6), and low-income countries (50% minimal and 50% intermediate care; estimated SMR 33·9).

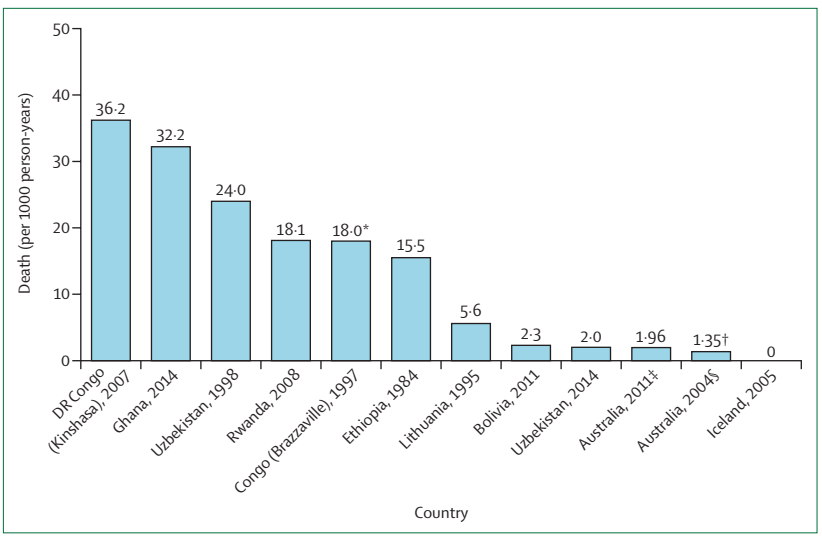

Figure 6: **Premature death in patients with type 1 diabetes diagnosed before the age of 40 years in different countries**

For the full references in this figure, see the appendix p 17. *Death related to the onset of diabetic ketoacidosis only. †Mean rates of men and women. ‡Aged younger than 30 years. §Aged 15–19 years.

By use of data on the incidence of type 1 diabetes from the International Diabetes Federation, population data and background mortality rate from the UN,[203,204] and data on age of diagnosis from different studies, we developed a discrete time Markov illness–death model[205] with age-dependent transition probabilities for all 220 countries listed in the *International Diabetes Federation Diabetes Atlas*. We estimated that 14466 young individuals with type 1 diabetes died in 2017 globally, from a total prevalence of diabetes in 1·61 million people. If all patients in LMICs had received an intermediate level of care with reduced SMR, 8369 deaths (58%) could have been averted. As many as 12092 deaths (84%) could have been averted if all nations had implemented guideline-based comprehensive care, resulting in a further reduced SMR (appendix pp 2–4).

Reducing diabetes-related complications by reducing multiple risk factors

Over the past three decades, prospective cohort analyses have reported the risk associations of blood glucose concentration, blood pressure, and LDL cholesterol concentration with cardiovascular disease and death in patients with type 2 diabetes.[206–208] These findings were followed by large-scale randomised controlled trials showing that sustained reduction of these risk factors for 2–5 years could substantially improve clinical outcomes in patients with type 2 diabetes. Subsequent meta-analysis of these randomised controlled trials substantiated that reduction of HbA_{1c} by 0·9% (10 mmol/mol),[209,210] systolic blood pressure by 10 mm Hg,[211] and LDL cholesterol concentration by 1 mmol/L (39 mg/dL)[212] individually reduced the risk of cardiovascular disease, all-cause death, or both, by 10–20%, independent of other risk factors.

In another meta-analysis, it was estimated that for every 200 patients with type 2 diabetes treated for 5 years, 14 myocardial infarction events could be prevented with a 4 mm Hg reduction in systolic blood pressure, eight events with a 1 mmol/L (39 mg/dL) reduction in LDL cholesterol concentration, and three events with a 0·9% (10 mmol/mol) reduction in HbA_{1c}.[209] Given the important role of the activation of the renin–angiotensin system in causing cardiovascular–renal diseases,[213] landmark studies have also supported the protective effects of renin–angiotensin system inhibitors in type 1[214] and type 2 diabetes,[215–217] especially in the presence of increased albuminuria.

Use of multifactorial management to achieve multiple treatment targets

Several randomised controlled trials have examined the control of multiple risk factors on cardiovascular–renal events and all-cause death, such as the ADDITION study, Steno-2 study, J-DOIT3 study, and SURE study. In the ADDITION trial, individuals were actively screened for type 2 diabetes followed by assignment to either intensive multifactorial or conventional treatment. After a mean follow-up of 5 years, there was no significant reduction in cardiovascular events in the intensive treatment group. Death rates were similar in both groups.[218] In the Steno-2 study, multifactorial management, including lifestyle intervention; control of blood glucose concentration, blood pressure, and LDL cholesterol concentration; and use of renin–angiotensin system inhibitors and aspirin (as appropriate) in patients with type 2 diabetes and microalbuminuria, without a history of cardiovascular–renal disease, reduced microvascular or macrovascular complications after 7·8 years. These outcomes translated into a long-term reduction in risk of end-stage kidney disease and all-cause death 10–20 years after completion of the trial.[219,220] The number needed to treat was 5–8 for death from any cause or death from cardiovascular cause, myocardial infarction, and stroke over 13 years. The number needed to treat for amputation was 10.[219] Subsequent economic analysis supported the cost-effectiveness of this multifactorial intervention when implemented in a primary care setting.[221]

In the SURE study involving patients with type 2 diabetes and chronic kidney disease, after receiving 2 years of team-based care with predefined processes aimed at controlling multiple risk factors, patients receiving structured care were 3 times more likely to reach multiple treatment targets with persistent use of renin–angiotensin system inhibitors than were patients in the usual care group. After just 2 years, patients who attained three or more treatment targets had 50% reduction in incidence of end-stage kidney disease and all-cause death compared with patients who attained fewer than three treatment targets.[222] Similarly, an analysis of real-world databases indicated the proportional and additive benefits of controlling HbA_{1c}, blood pressure, and LDL cholesterol concentration on reducing cardiovascular–renal diseases in type 2 diabetes, whereby lowering LDL cholesterol concentration with statins had the greatest effect size.[223–225] In the latest analysis of the Swedish National Diabetes Register involving over 200 000 patients with type 2 diabetes, there were linear relationships between the number of cardiometabolic–renal–behavioural risk factors attained (defined as HbA_{1c} <7·0% [53 mmol/mol], blood pressure <130/80 mm Hg, LDL cholesterol concentration <1·8 mmol/L [70 mg/dL], no smoking, and microalbuminuria), and cardiovascular events and related death.[226,227]

Stratifying risk to maximise benefits and to minimise harm of lowering blood glucose concentration

In the UKPDS[228] started in 1977, having an HbA_{1c} of 7·9% (63 mmol/mol) with conventional glycaemic control strategies versus 7·0% (53 mmol/mol) with intensive strategies in type 2 diabetes reduced the risk of microvascular complications in the short term and cardiovascular complications in the long term. Similarly, in the DCCT[229] started in 1983, an HbA_{1c} of 9·0% (75 mmol/mol) with conventional glycaemic control strategies versus 7·0% (53 mmol/mol) with intensive strategies in type 1 diabetes reduced these complications. Post-hoc analysis identified the close relationship between HbA_{1c} and diabetes-related complications, which provided the premise for three landmark studies in 2000 that aimed to reach lower HbA_{1c} values than those seen in the UKPDS and DCCT.

In all three trials, namely the ACCORD,[230] VADT,[231] and ADVANCE trials,[232] most participants were aged older than 60 years and had over 10 years of diabetes with multiple risk factors and complications. All three trials had similar design and outcome measures, and a mean HbA_{1c} of 6·4–6·9% (46–52 mmol/mol) during the trial period. Although all trials accorded with a reduced risk of microvascular complications in the group of patients receiving intensive treatment, the results for cardiovascular death were controversial with premature discontinuation in the ACCORD study due to unexpected increased risk of death in this treatment group. These results triggered intensive research that highlighted the high risk of hypoglycaemia in patients with multiple morbidities, especially chronic kidney disease, after long disease duration. The silent deterioration of renal function coincides with progressive atherosclerosis in patients with long disease duration. The frequent coexistence of cardiovascular disease and chronic kidney disease puts these patients, who often receive complex therapies, at high risk of hypoglycaemia, which might precipitate cardiovascular disease or identify patients with a frail phenotype.[233–235] These observations have led to changes in practice guidelines, calling for regular assessment of risk factors and complications for the

individualisation of treatment targets and strategies to lower blood glucose concentration, which consider the demographic, biomedical, cognitive, psychosocial, and behavioural profiles of patients to maximise benefits and to minimise harm.[236–238]

Effective use of glucose-lowering drugs: old versus new therapies

Together with insulin, first discovered in 1922, metformin and sulfonylurea (discovered in the mid-1950s) have been the standard drugs for lowering blood glucose concentration. Generally these drugs are effective, albeit not without side-effects. Except for insulin, which can lower blood glucose considerably, most of these medications reduce HbA_{1c} by 0·5–1·0% (5·5–11·0 mmol/mol) on average.[239] However, drug responses vary considerably between individuals,[240] depending on other factors pertinent to hosts and settings. Patients with high HbA_{1c} often have the greatest response, partly due to the drug ameliorating the effects of glucotoxicity on β-cell function. Nevertheless, these patients also have the most residual glycaemic burden, requiring additional interventions.[241] With data from long-term and short-term trials, researchers have reported strong correlations between cumulative glycaemic exposure and clinical outcomes, and between differential glycaemic exposure and reduction in the risk of cardiovascular disease. Thus, if therapy to lower blood glucose concentration could be initiated early and sustained with a low risk of hypoglycaemia, long-term benefits could ensue, even with traditional drugs (eg, metformin and sulfonylurea),[242] as reported by the UKPDS.[228]

Insulin and sulfonylurea have potent effects on lowering blood glucose concentration but might cause clinically significant hypoglycaemia that can lead to hospitalisation,[234,243,244] morbidity, and premature death, especially in patients with frailty and multiple morbidities.[245] These adverse effects have led to the emphasis of periodic assessments and education to deliver individualised care centred around the patient, considering the risk of hypoglycaemia, comorbidities, obesity, and economics. During the past three decades, the pharmaceutical industry has invested heavily to develop new medications to lower blood glucose concentration safely without weight gain and hypoglycaemia. The multiple sites of action of these medications (including islets, gut, brain, muscle, adipose tissues, liver, and kidney) have been extensively reviewed.[246] Suffice to say, this diversity reflects the complex regulation of glucose homoeostasis that involves multiple pathways, which has led to the development of various glucose-lowering drugs with different extraglycaemic effects.

Among different classes of drugs, the cardiovascular–renal protective effects of SGLT2 inhibitors and GLP-1 receptor agonists, independently to their properties of lowering blood glucose concentration, have now been substantiated, providing health-care providers with additional armamentarium in managing these patients at high risk.[247] However, the high price of these new medications has restricted their affordability in resource-limited settings. The efficacy, safety, and low cost of metformin, as well as the cardiovascular safety of sulfonylurea compared with DPP-4 inhibitors,[248] have reassured the community regarding the clinical value of metformin and sulfonylurea, which are widely used in LMICs.[239] As new medications (eg, SGLT2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists) increase in affordability, the landscape of glucose-lowering drugs might change, considering their organ protective effects, glycaemic durability, and cost-effectiveness in the long term.[249] In this light, young patients who face decades of hyperglycaemia and have a high lifetime risk of developing complications might benefit most from these drugs with low risk of hypoglycaemia and weight gain.[55] However, evidence from randomised controlled trials is needed to inform treatment guidelines.[79]

Diagnosing and treating diabetes early to induce remission and to improve glycaemic durability for improved outcomes

Reduced early phase insulin secretion and non-suppression of glucagon,[90] followed by progressive decline in β-cell function,[250] is a hallmark of impaired glucose tolerance and type 2 diabetes. In the UKPDS, age of diagnosis, obesity (general and central), baseline plasma glucose concentration, and triglyceride concentration were predictors of progressive β-cell failure and treatment escalation.[251] In a proof-of-concept study, researchers reported sustained recovery of insulin secretion at 2 years after 2 weeks of intensified insulin treatment in patients with type 2 diabetes.[252] In the DiRECT study,[253] a weight management programme in a primary care setting involving 298 patients with type 2 diabetes who had less than 6 years of disease and a BMI of 27–45 kg/m² (mean BMI 35·1 kg/m²), 149 individuals were randomly assigned to receive an intervention with severe and structured dietary restriction and 149 others were given usual care. 1 year after the intervention, 68 patients (46%) in the intervention group had diabetes remission (defined as HbA_{1c} <6·5% [48 mmol/mol] without medications) and 36 patients (24%) had at least 15 kg of weight loss. Among patients with 15 kg of weight loss or more, 31 individuals (86%) had diabetes remission. 2 years after the intervention, 17 patients (11%) in the intervention group and three patients (2%) in the control group had at least 15 kg of weight loss, and 53 patients (36%) in the intervention group and five patients (3%) in the control group had diabetes remission.[254] In a post-hoc analysis of the whole study cohort, 29 (64%) of those participants who maintained at least 10 kg weight loss (45 of 272 patients with data) had remission and 36 (24%) of 149 participants in the intervention group maintained at least 10 kg weight loss.[254] By use of an arginine stimulation test, patients who had diabetes remission showed a similar peak and

first insulin response to individuals with normal glucose tolerance, suggesting restoration of β-cell function after substantial weight reduction.[255] Despite these encouraging results, the sustainability and long-term effects of intensive weight loss interventions on remission needs further research.

Although many patients with diabetes have obesity, some individuals do not,[256] in whom early amelioration of glucotoxicity might improve glycaemic durability. In the VERIFY study, researchers compared the strategy of early intensive treatment using combination therapy (ie, metformin plus DPP-4 inhibitors) versus metformin monotherapy in reducing the likelihood of primary and secondary treatment failure in patients newly diagnosed with type 2 diabetes. In this 5 year study, involving 2001 patients with type 2 diabetes who had a disease duration of 3 months, mean HbA_{1c} of 6·7% (50 mmol/mol), and mean BMI of 31 kg/m², combination therapy reduced the risk of poor glycaemic control (HbA_{1c} >7% [53 mmol/mol] on two occasions 3 months apart) by 49%, compared with monotherapy. The time to poor glycaemic control was 36 months in the group receiving monotherapy, compared with 61 months in the group receiving combination therapy. With early intensified treatment, patients receiving combination therapy were 27% less likely to require insulin therapy than were patients receiving monotherapy, who subsequently also received DPP-4 inhibitors.[257]

The glycaemic legacy effect of early intervention in newly diagnosed patients in the UKPDS[228] and in individuals with impaired glucose tolerance in a diabetes prevention programme[258] has led to long-term reduction of cardiovascular–renal events and all-cause death. Together with the results from the DiRECT and VERIFY studies, the use of a system-wide strategy to diagnose and treat patients with type 2 diabetes early and intensively might induce remission or maintain glycaemic durability with long-term benefits, additionally to the use of other medications for organ protection.

Self-management, regular monitoring, and feedback are key factors in diabetes care

In addition to smoking, blood pressure, LDL cholesterol concentration, HbA_{1c}, and bodyweight are among the most modifiable risk factors in diabetes. However, HbA_{1c} and bodyweight modifications require considerable behavioural changes and self-management. The results of the DiRECT study led by primary care physicians indicated that substantial weight reduction with discontinuation of multiple medications is possible,[253] if patients are given adequate support and supervision. Although these results are extremely encouraging, many patients with type 2 diabetes have long disease duration or poor β-cell function, making remission challenging. Besides, innovative and context-relevant implementation programmes are needed to scale up the operation in identifying suitable patients to participate in this intensive weight reduction programme, with evaluation of its cost-effectiveness.

Irrespective of the causes of type 1 and type 2 diabetes, when the machinery of glucose sensing and insulin secretion is dysregulated, any changes in daily activities including, but not limited to, diet, exercise, concurrent illness, sleep, and emotions can cause wide fluctuations in blood glucose concentration, depending on disease stage and treatment.[259] Without proper professional training and structured patient education and support, patients and health-care providers alike will find it difficult to explain these fluctuations in blood glucose concentration and to take corrective actions. Patient dissatisfaction and distress can lead to frustration and burnout for health-care providers, resulting in poor patient–provider relationships, which in turn can worsen treatment adherence and quality of care.[37,41,260] Training of health-care providers in psychological health and behavioural science will help them to design, implement, and evaluate patient empowerment programmes needed to promote self-management.[261]

In the UKPDS, after the initial 2% reduction in HbA_{1c} there was a progressive upward drift,[262–264] partly due to ongoing glucolipotoxicity with progressive β-cell dysfunction.[265,266] These findings have been substantiated in large-scale surveys of type 2 diabetes, showing loss of glycaemic control over time.[251,267] Similarly, blood pressure tends to rise with increasing disease duration.[267] Ageing aside,[268] irregular monitoring, medication non-adherence, and delayed treatment intensification all contribute to progressive loss of control of these risk factors in patients with type 2 diabetes in real-world practice.[269] In several surveys, fewer than 50% of patients had their treatment intensified, even though they had been suboptimally managed for more than 7 years.[270,271] However, fewer than 50% of patients adhered to or persisted with their therapies, resulting in treatment failure and high costs, mainly due to hospitalisations and acute emergencies.[272,273] In a meta-analysis, after an initial fall in HbA_{1c} of 0·76% (8·3 mmol/mol), HbA_{1c} started to increase by 0·26% (2·8 mmol/mol) at 1–3 months, and by another 0·26% (2·8 mmol/mol) in the subsequent follow-up period of 4 months or more. Researchers estimated that an average of 23·5 h of contact time during a 12 month follow-up period was needed to sustain a 1% (11 mmol/mol) reduction in HbA_{1c}.[274,275] By reorganising care with non-physician personnel and technology,[276] the efficiency of care delivery can be improved to address the psychosocial and informational needs of patients and to improve self-care and treatment adherence, especially in individuals who have not yet developed complications and who might have low motivation to change their habits.[277]

Variations in quality of care and clinical outcomes mean that control of diabetes is achievable

In a 12 year survey, consisting of seven different cohorts of patients with type 2 diabetes totalling 66 088 participants recruited by 6099 physicians from 49 countries outside of

North America and western Europe, the proportion of patients with HbA_{1c} less than 7·0% (53 mmol/mol) decreased from 3570 (36·0%) to 1897 (30·1%) between 2005 and 2017.[278] In another multicentre survey involving 10 000 patients from outside the USA and Europe, only 20–30% of people with type 2 diabetes attained recommended HbA_{1c} (<7·0% [53 mmol/mol]), blood pressure (<130/80 mm Hg), and LDL cholesterol

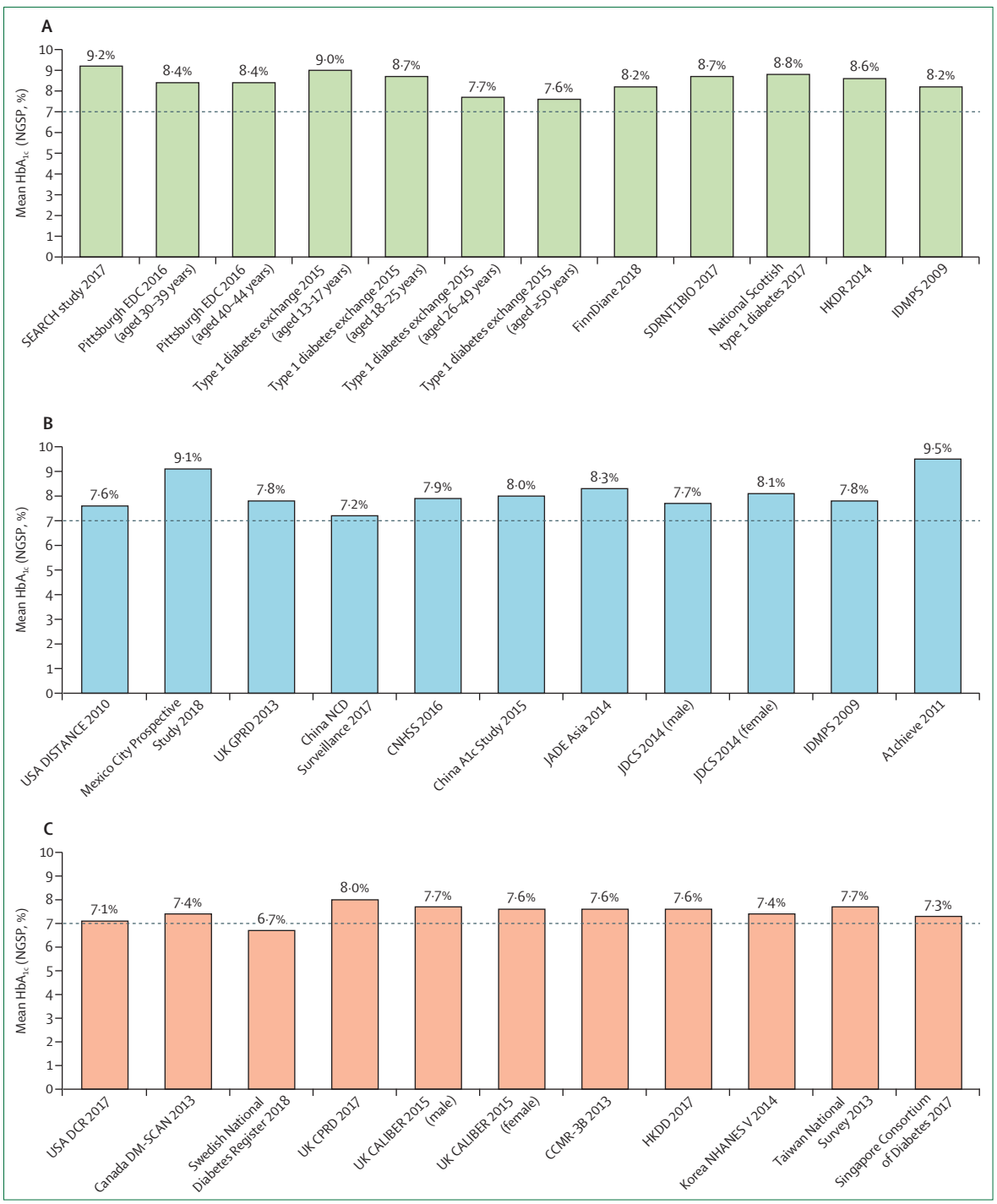

Figure 7: **A global landscape of HbA_{1c} in 1·9 million people with diabetes from 26 cohorts**
Mean HbA_{1c} was measured in a cohort with type 1 diabetes (A) or type 2 diabetes aged younger than 60 years (B) or 60 years and older (C). Each cohort had at least 5000 patients. High concentrations of HbA_{1c} were observed especially in patients with type 1 diabetes and young patients with type 2 diabetes. For the full references in this figure, see the appendix pp 18–19. HbA_{1c}=glycated haemoglobin A_{1c}. NGSP=National Glycohemoglobin Standardization Program.

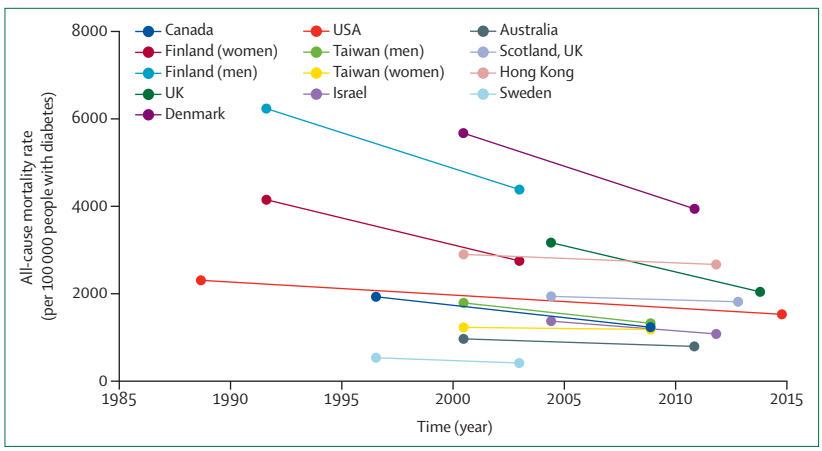

Figure 8: **Trends in all-cause mortality among people with diabetes by country or region, 1988–2015**
These data are from high-income countries, showing a paucity of similar data in low-income and middle-income countries. Reproduced from Harding et al,[280] by permission of Springer. For the full references in this figure, see the appendix p 20.

concentration (<2·6 mmol/L [100 mg/dL]) targets, and only 5–10% of the patients met all three targets. On average, only 20–50% of patients were treated with organ-protective drugs (notably statins and renin–angiotensin system inhibitors), or underwent periodic eye and foot examination and blood or urine testing in accordance with international recommendations.[279] By curating data from 40 surveys consisting of 1·9 million individuals recruited from HICs and LMICs, with each study enrolling at least 5000 patients with either type 1 or type 2 diabetes, only 20–40% of individuals had HbA_{1c} less than 7% (53 mmol/mol).[239] Furthermore, patients with type 1 diabetes and young patients with type 2 diabetes had worse glycaemic control than did adults with type 2 diabetes, highlighting failure of health-care providers and systems to translate evidence to benefit the larger community (figure 7).

In HICs, where access to care, education, and medications are covered by either general government funding or public or private health insurance schemes, there have been notable improvements in terms of health-care services and reduction in risk factors, complication rates, and death rates (figure 8). In the USA between 1990 and 2010, acute myocardial infarction events decreased by 67·8%, death from hyperglycaemic crisis by 64·4%, stroke incidence by 52·7%, lower extremity amputation by 51·4%, and incidence of end-stage kidney disease by 28·3%. The reduction in vascular and renal outcomes was greater in patients with diagnosed diabetes than in individuals who did not have diabetes.[21] During the same period, attainment of HbA_{1c}, blood pressure, and LDL cholesterol concentration treatment targets improved by 7–10%, although 33·4–48·7% of patients with diabetes still did not meet any of these targets. Based on patients self-reporting, there were also moderate improvements in foot examination and annual measurement of serum lipid concentration, and few improvements in annual eye and dental examinations.[281,282]

In an analysis of the Hong Kong Diabetes Database,[267] a territory-wide register of 338 900 Chinese patients with type 2 diabetes who had structured assessment (eg, eye, feet, blood, and urine) every 2–3 years in publicly funded health-care institutions with access to education and medications, there were clinically significant improvements in risk factor control and increased use of statins and renin–angiotensin system inhibitors between 2002 and 2012. The proportion of patients with HbA_{1c} less than 7% (53 mmol/mol) increased from 32·9% to 50·0%, blood pressure equal to or lower than 130/80 mm Hg from 24·7% to 30·7%, and LDL cholesterol concentration lower than 2·6 mmol/L (100 mg/dL) from 25·8% to 38·1%. Among patients with diabetes for 15 years or more, the crude incidence of acute myocardial infarction decreased from 8·7 to 5·8, stroke from 13·5 to 10·1, end-stage kidney disease from 25·8 to 22·5, and death from 29·0 to 26·6 per 1000 person-years between 2000–02 and 2010–13. These improvements remained significant after adjustment for baseline risk profiles and were attenuated only after adjustment for enrolment years for structured assessment, suggesting that this territory-wide risk assessment and management programme has led to corrective actions with improved outcomes.[267] In the latest analysis of over 770 000 adults with type 2 diabetes observed between 2001 and 2016, death decreased by 52·3% in men and 53·5% in women from all causes, by 72·2% in men and 78·5% in women from cardiovascular disease, and by 65·1% in men and 59·6% in women from cancer.[59] However, the reduction was less evident in young adults aged 20–44 years than in adults aged older than 45 years.

There are considerable variations between and within countries in the care cascade from awareness, diagnosis, and treatment to control in LMICs and HICs.[283] However, on average, the 2–3 times higher and rising incidence of cardiovascular disease and death rates in LMICs (eg, India), compared with the decreasing rate of cardiovascular disease in North America,[163] might reflect differences in resources, capacity, access, and care organisation. The close association between reduction in risk factors and clinical outcomes in randomised controlled trials and real-world settings provides a strong business case for investing in preventive care by controlling multiple risk factors and by empowering patients. These efforts can yield high return after 10–15 years by reducing long-term complications (ie, pay now, save later, rather than save now, pay later).[284] In 2010, the USA spent US$7383 per capita adjusted for purchasing power for treating diabetes, mainly comorbidities, compared with less than $100 per capita in 16 low-income countries. The USA spent 52·7% of global expenditure on diabetes, whereas India spent less than 1% of the world's total expenditure, despite having one of the largest populations of patients with diabetes. In total, all 18 countries included

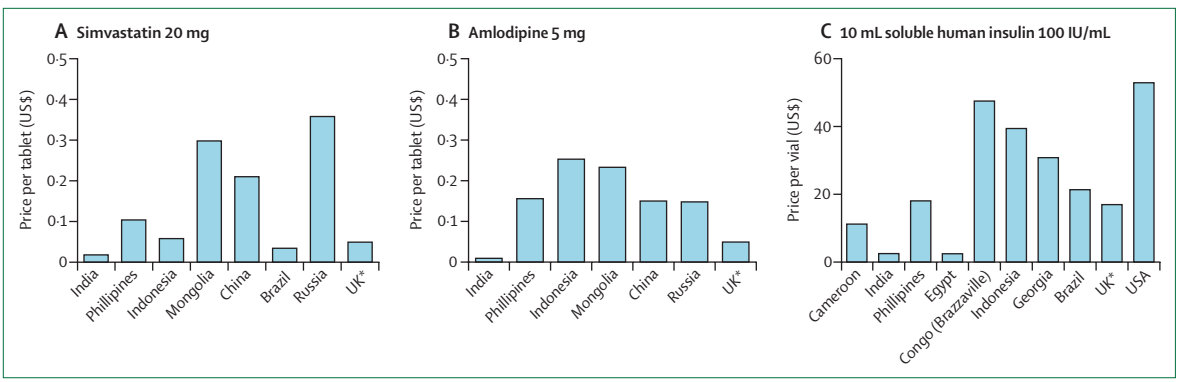

Figure 9: **Price differences in common medications used in patients with diabetes**
Countries ranked on the basis of gross domestic product per capita in 2011. Prices of simvastatin (A) and amlodipine (B) are public sector procurement prices from various surveys done by the collaborative partnership between WHO and Health Action International in the project on medicine prices and availability from 2002 to 2013.[297] Data on insulin (C) are private prices based on a global snapshot on May 11, 2010, as reported by WHO—Health Action International. *UK prices are based on Category M (retained margin) price.[298]

in the African region, as defined by the International Diabetes Federation, spent only 0·3% of global diabetes expenditure.[159]

Importance of context-relevant data to guide local practice and policies

Distribution of resources is often a political decision, rather than one based on evidence. In LMICs where local data are frequently scarce, funding bodies often have to find the right balance between investing in preventive care for future gains and providing care to patients with more immediate needs. Use of medications is essential to diabetes management. Currently, most economic evaluations in diabetes focus on drugs and devices that lower blood glucose concentration (eg, insulin-based treatment regimens),[285] and on interventions aimed at improving other aspects of risk factor control.[286] A growing number of countries are allocating public funds to interventions based on cost-effectiveness,[287,288] which depend on incremental cost and health benefits, often expressed as quality-adjusted life-years. These analyses often influence reimbursement decisions for pharmaceuticals[289] and, to a lesser degree, medical devices,[290] and systems of payment of health-care providers.[291] Beyond treatment, there are also economic evaluations of preventive interventions targeting specific populations at high risk,[292] and those targeting the broader community.[293]

Escalating costs of medications and lifelong care suggest a need to improve efficiency in care delivery

In the absence of country-specific data on cost-effectiveness from LMICs, economic evaluations derived from HICs[286] and international randomised controlled trials are sometimes used to guide clinical decision at a national level.[294] These analyses suggested that control of blood glucose concentration with metformin, sulfonylurea, and insulin is cost-effective and recommended by WHO.[248] Large randomised controlled trials also supported that control of blood pressure[295] and LDL cholesterol concentration[296] are cost-effective and, in some cases, cost saving. With the expiry of patents, the cost of many widely used therapies (eg, oral glucose-lowering drugs, statins, and angiotensin-converting enzyme inhibitors) has fallen markedly, increasing the cost-effectiveness and affordability of these therapies on a global basis. In many countries, generic drugs for treating individuals with diabetes can be purchased for just a few cents per day. However, surveys of drug prices have indicated wide variations across and within countries (figure 9). These price differences (eg, for insulin) are often related to the supply chain structure; mark-up by distributors, wholesalers, and retailers; and, occasionally, import duties.[299]

In areas where large variations exist in costs between different types of therapies (eg, classes of glucose-lowering drugs), there is a need to assess whether or not expensive therapies provide additional benefits that justify the high cost. In some countries, national health services and country-wide coverage schemes have enabled effective negotiations to ensure equitable returns for manufacturers, while retaining security of supply to the consumer. The most cost-effective strategies to control diabetes and reduce complications might change over time, purely due to changes in the relative cost of therapies, which might influence future practice guidelines.

Although new technologies, including insulin analogues and pumps, have the potential to improve and extend the lives of people with type 1 diabetes, most come at a higher cost than the interventions they replace. Globally, the cost of human insulin varies greatly, especially in LMICs.[300,301] For example, data collected by Health Action International indicated that the price a patient would have to pay for a 10 mL vial of soluble human insulin ranged from US$1·55 to $76·69 across different countries.[302] In a survey involving 13 LMICs, up to 80% of countries (10 countries) have access to human insulin compared with 60% of countries

(7 countries) having access to insulin analogues, which are 3 times more expensive, especially in the private market.[180] Researchers estimated that a person on low income had to work 4 days to buy 10 mL of human insulin and 7 days to buy 10 mL of insulin analogue. The high costs of medications and accessories are often due to complex procurement and distribution involving multiple parties. Enactment of policies aimed at increasing price transparency; encouraging competitions among manufacturers; reducing unnecessary administrative costs; promoting use of quality-assured, generic medications, including biosimilars; or providing a subsidy for medications with a ceiling of out-of-pocket payments through public–private partnership might increase the accessibility and affordability of preventive care, and reduce the financial impact on patients and their families.[185]

Although there are several strategies to promote insulin access in LMICs,[303] lessons can be learned from global efforts to tackle infectious diseases, such as HIV, malaria, and tuberculosis. In these affected areas, global funds have been established by donors to finance innovative research.[304] With diabetes, patients need access to affordable ways to monitor blood glucose concentration.[182] A prize to reward such innovations might replace traditional patent systems to increase their affordability.[305] Nevertheless, these propositions can have challenging economic and moral issues, including finding a balance between cost and quality. Besides, the implementation of these funding schemes have been met by multiple issues, including logistics, monitoring of milestones and performance indices, and fund management.[304]

Closing gaps in medical coverage, care organisation, and care continuity

Insufficient patient engagement and care fragmentation often lead to suboptimal control of risk factors, resulting in complications that substantially increase health-care costs.[306,307] Health-care provision and financing are complex issues that need to be relevant to various contexts. An analysis of the 2002–2003 World Health Survey data indicated that patients with diabetes spent considerably more on out-of-pocket medical expenses and had a greater chance of incurring substantial medical expenses than did individuals without diabetes.[308] In general, without adequate insurance coverage or national provision of good outpatient care, including consultations, medications, and investigations, many patients are not willing to pay out of pocket for preventive care. This behaviour is often due to non-urgency or vague symptoms, and can result in missed opportunities of early intervention.[309] In LMICs, patients with diabetes have a much higher out-of-pocket cost than do individuals with diabetes in HICs.[310] In low-income countries, out-of-pocket costs accounted for 43–100% of the health-care spending. In the USA, over 90% of patients with diabetes had health-care insurance and their out-of-pocket payments accounted for 0–13% of total health expenditure (table 1). However, for some high deductible insurance schemes or medical saving account schemes, the need to co-pay might represent a barrier to seeking preventive care, especially in low-income populations.[311]

In many patients with diabetes, inability to obtain adequate insurance coverage means that even patients with reasonable income might suffer huge financial losses when these complications develop.[312] A 2008 decision by Oregon, USA, to expand its Medicaid Programme gave researchers the opportunity to evaluate the effects of expanding insurance coverage. The results indicated that people who received insurance had a greater probability of being diagnosed and receiving medications for diabetes than did individuals without insurance.[313] Similarly, among adults with diabetes in the USA, acquiring Medicare insurance coverage was associated with an increase in visits to the physician.[314] There is also evidence from outside the USA that insurance positively affects health-care use. In Mexico, the introduction of public health insurance (so-called Seguro Popular) has led to an increase in the use of insulin and oral medications in patients with diabetes;[315] however, the effects of insurance on disease control for patients with diabetes is mixed.[313]

In Japan, which has a system of universal health coverage, quality indicators vary considerably, such as assessment for complications and risk factors, attainment of treatment targets, and use of life-saving medications, with improved performance among institutions with certification.[316] In some HICs, as many as 50% of patients did not complete follow-up visits, especially patients who were young, newly diagnosed, or both. These patients were more likely to have poor control of risk factors, develop complications, attend emergency departments, or require hospital admissions than were patients receiving continued care.[317–319] In a survey involving patients with type 2 diabetes from HICs (eg, Australia and France) and low-income and middle-income regions (eg, Latin America), the proportion of patients receiving recommended care processes and reaching recommended treatment targets remained remarkably similar, despite marked differences in national health-care investment.[320] These data suggested that, health-care investments aside, care organisation aimed at improving access and reducing default are important determinants for outcomes. Professional training, patient education, and registers are additional strategies needed to add value to care delivery, with exemplary examples in LMICs and HICs.[321]

Mandates, incentives, and audits are universal pillars in health-care reform, applicable to most health-care systems.[322] These strategies can be used to guide payers and users to distinguish between high-value and low-value services, supplemented by payment schemes to encourage the provision and subscription of services

with added value.[323] In areas where private and public sectors provide health care, alignment among payers, patients, providers, and industry might allow efficient use of emergency, inpatient, and outpatient care in both sectors.[324] In Argentina, medication costs for patients with type 2 diabetes were driven by long disease duration and complex therapies, although good glycaemic control reduced overall cost.[325] A multistaged quality improvement programme aimed at enhancing professional knowledge, patient self-management, and access to medications in primary care settings, supplemented by registers for quality assurance, improved clinical outcomes and saved costs.[326] In the UK, introduction of the Quality and Outcomes Framework in primary care with financial incentives has led to improvements in process and outcome measures.[327] In Asia, several governments, including those in China, Taiwan, Hong Kong, and Singapore, have adopted a data-driven strategy by providing or subsidising structured risk assessment, education, and management programmes.[328,329]

Interventions for prevention of type 2 diabetes directed at populations and individuals at high risk

Given the life-course and multidimensional nature of diabetes (including environmental and lifestyle factors), a multipronged, multitiered, and multisectoral strategy is essential to prevent and manage the disease. This strategy includes, but is not limited to, use of fiscal measures to protect the environment with improved city planning, control of emission of air or water pollutants, regulation of food safety and quality, introduction of sugar tax, designation of tobacco-free public areas, and creation of healthy cities with increased space to promote physical activity and recreational activities. Low education and health illiteracy are major barriers to risk awareness and behavioural change. As such, raising the level of general educational attainment through provision of secondary school education, and increasing health education in early school curriculum might improve health literacy and help to raise awareness on diabetes. Furthermore, improvements to maternal and child health have an important role in the life-course prevention of diabetes, although more research is needed to identify mothers and children at high risk for targeted interventions.[330]

Societal measures aimed at improving the wider determinants of health-related behaviours are in accordance with the UN SDGs, in which quality education, environmental and social protection, and an appropriately functioning health-care system are key to a sustainable economy. Practitioners, researchers, and managers, who have expert knowledge in the multidimensional nature of diabetes and the local and complex needs of individuals with or at risk of having diabetes, are in a unique position to use research, best practices, and dialogues to inform policy makers, corporations, and the civic community. These concerted actions are needed for designing, implementing, and evaluating a context-relevant and integrated society–population–community strategy aimed at changing the ecosystem, improving the health-care environment, and ensuring health-care equity for preventing and controlling obesity, diabetes, and other NCDs.[331]

Preventing type 2 diabetes can prevent cardiovascular disease: challenges and opportunities

Several randomised controlled trials and meta-analyses have substantiated that type 2 diabetes can be prevented by lifestyle interventions in closely supervised situations.[332–336] In China, lifestyle interventions in middle-aged individuals (mean age 45 years) with impaired glucose tolerance reduced conversion to type 2 diabetes by 40% at 6 years. After the study was completed, the intervention group continued to benefit from a 20% risk reduction of retinopathy, cardiovascular disease, and all-cause death 30 years after the trial commenced.[258] The benefits of lifestyle interventions with or without medications (including metformin, α-glucosidase inhibitors, and thiazolidinediones) in reducing the onset of type 2 diabetes in individuals with impaired glucose tolerance and multiple cardiometabolic risk factors have also been reported in studies from the USA, Europe, India, and Japan. Similarly, lifestyle interventions also reduced hypertension in individuals without impaired glucose tolerance.[337,338] This evidence has led to the establishment of systematic, individual-level prevention programmes for people at high risk of type 2 diabetes in HICs, such as Germany, Finland, the USA, the UK, Poland, and Singapore. Real-world implementation of these lifestyle intervention programmes with reduced intensity has yielded favourable results across Asia, Africa, and the Middle East (table 3).

Translating evidence to practice should consider the absolute risk of future type 2 diabetes in an individual, and the risk reduction that can be achieved by the intervention. These parameters form the basis of absolute risk reduction (ie, difference in event rates between control and experimental groups), and the number needed to treat (ie, inverse of absolute risk reduction). Thus, for the same risk reduction, individuals at high risk will gain more from the intervention, with a lower number needed to treat to have positive outcomes, than will individuals at moderate risk of diabetes. Countries that have translated this evidence often adopt an integrated approach of establishing guidelines; training an effective workforce of non-physician personnel, lifestyle coaches, and various types of health-care providers; monitoring quality through simple registers; encouraging reimbursement; raising awareness; and marketing programmes.[341,342] To date, the evaluation of the National Diabetes Prevention Programme in the USA has shown a rapid increase in trained lifestyle

	Diet	Physical activity
Supranational	International trade agreements on food, food-related commodities, and agriculture	International trade agreements on automotive industry; international agreements on climate change
National	Taxes on unhealthy foods levied on producers or consumers and subsidies on healthy foods; reformulation of commercially produced food to reduce density of less healthful nutrients; restricted marketing of unhealthy foods on television and online; mandatory food labelling of nutrients and calories on packaging and menus; mandatory restriction of marketing of unhealthy foods within stores (eg, price promotions, placement, volume discounts); industry-led reduction in portion size for packaged food and food served ready to eat	Taxes on transport mode (eg, fuel duty); subsidies to promote healthy travel (eg, bike-to-work schemes and subsidised public transport)
Regional	Regional school food policies (eg, breakfast programmes and food and nutrition standards); healthy food policies in other publicly funded spaces (eg, recreational settings, hospitals, government employers); regional social marketing and mass media campaigns	School sports funding and organisation (eg, school sports partnerships); regional taxes or subsidies on transport mode; regional social marketing and mass media campaigns
Local	Locally restricted marketing of unhealthy foods in schools, outdoors, and in recreational settings; use of planning systems to regulate food outlets selling or serving food of differential healthfulness	Promotion of walking and cycling infrastructure; development of local space for physical activity (eg, parks, leisure centres, playing fields); use of local planning regulation to promote walkable neighbourhoods; use of local fiscal levers to promote healthy travel (eg, subsidised public transport, parking charges, and congestion charging); physical activity promotion programmes based in schools
Community	Faith-based cooking or food interventions	Faith-based physical activity interventions
Individual	Individual, group, or digital dietary interventions	Individual, group, or digital physical activity interventions

Interventions taken from WHO's *Best Buys*,[339] the UN Sustainable Development Goals,[339] and WHO Convention Framework for Control of Tobacco.[340] Educational policies should be implemented at all levels to improve literacy, self-management, and lifelong coping skills. Environmental policies are important for building smoke-free, healthy cities with clean air, water, and foods. Social policies reduce poverty and inequalities, and ensure care equity. These interventions require a combination of government leadership, intersectoral collaborations, and community mobilisation.

Table 3: **Consensus recommendations of interventions for possible use as part of an integrated approach to type 2 diabetes prevention**

coaches and participation, and favourable weight loss of 4% at 1 year, which is generally in line with the magnitude of weight loss observed in community translation trials.[341,342] This programme has also achieved health-care coverage policies that had not been previously achieved. Similar efforts are now underway in the UK, following support and recommendation of the National Health Service.[343]

Compared with research settings that are often confounded by volunteer bias and close supervision, the uptake of screening and intervention programmes and the intensity of interventions in real-world practice is often not as high.[344] In the USA, the MOVE-IT trial[345] used group motivational interviewing delivered by non-physician personnel to reduce cardiovascular risk in individuals with a 10 year risk score of 20% or more for future cardiovascular disease identified during routine health checks. Although lifestyle interventions worked in the group of individuals who were adherent and who completed a programme of intense and sustained intervention, these participants represented only a small proportion of the population for whom the intervention was designed. Other barriers in implementing primary prevention programmes include economic constraints, insufficient resources, cultural taboos, poor health-seeking behaviour, and inadequate knowledge and skills.[346] To this end, some researchers used behavioural economics, such as providing financial incentives to increase physical activity, use of visual cues to encourage selection of heathy food choices, or retracting deposits from patients for not reaching targets in a contract of weight reduction.[347] These studies have yielded encouraging results, suggesting that similar approaches can be further explored.

A crucial element of any scaled up, individual-level prevention strategy is the efficient identification of individuals at a sufficiently elevated risk of future diabetes to warrant intervention. Methods commonly used include word of mouth, information through flyers and posters, advertisement, recruitment through existing programmes, holding community screening programmes, recruiting selective populations (eg, by use of risk scores), and targeting family members of patients and staff of corporations. Few studies have examined the most effective approaches for identifying individuals at high risk, relevant to the local population and health-care setting. It is also unknown whether or not approaches that work in HICs, with generally high literacy and well supported primary care systems, are translatable to other settings where illiteracy and availability, or access to primary care are important barriers. These challenges have fuelled new research into the science of engagement and uptake, as well as tailored modalities of delivery to optimise participation and effectiveness. In a meta-analysis of real-world programmes for type 2 diabetes prevention, group intervention with community health workers or professionals were similarly effective, with weight loss as the major determinant closely associated with levels of engagement.[348] Therefore, by developing and evaluating innovative multicomponent care models including, but not limited to, technology and trained community health workers or peers linked to health-care systems, these challenges are not insurmountable.

Use of technology and non-physician personnel might enhance the cost-effectiveness of lifestyle interventions

In a systematic analysis of 28 studies, the economics of lifestyle intervention programmes done mainly in HICs, consisting of at least two sessions in 3 months delivered to people at increased risk of developing diabetes, were analysed in 2013. The median programme cost per participant was US$653, with lower costs for group-based programmes ($417) and community-based or

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primary care-based programmes ($424). This cost compares with $5881 per participant for the DPP trial and the DPPOS.[349] From a health-system perspective, the median incremental cost-effectiveness ratio was $13 761 per QALY saved. Group-based programmes were more cost-effective ($1819 per QALY) than individual-based programmes ($15 846 per QALY).[349] In a 15 year analysis of the DPP and DPPOS, which also included a metformin intervention group, metformin was found to be cost saving in preventing diabetes with reduced long-term complications, especially among individuals with obesity, high fasting plasma glucose concentration, or a history of gestational diabetes.[350]

As a general rule, interventions are more cost-effective when the intervention is targeted at individuals who are at a high absolute risk of type 2 diabetes,[351] and when the interventions are delivered in a group format by trained community health workers or peers. The advent of mobile health programmes offers an opportunity for developing potentially scalable and cost-effective management strategies for prevention of diabetes and other NCDs, especially in LMICs.[352] In India, an SMS study that used mobile phones to provide health behaviour messages to men with impaired glucose tolerance found a 36% relative risk reduction in the development of type 2 diabetes after 2 years.[353] Since then, national programmes have been introduced in 11 states where nodal centres have been established to train physician and non-physician personnel in the early detection, management, and prevention of type 2 diabetes. It is expected that trained personnel will disseminate knowledge to the local community by organising awareness programmes. Similarly, promising approaches based on online and social media platforms that support lifestyle changes are underway, but data on the long-term outcomes of these programmes from randomised controlled trials are scarce.

In a multicentre study done in South America, a 12 month, phone-based health intervention that used monthly motivational counselling calls and weekly personalised text messages resulted in meaningful reduction in blood pressure and bodyweight that was sustained after 6 years, especially among participants who engaged with at least 50% of the calls.[354,355] The use of information and communication technology, such as wearable devices to monitor physical activity, sleep pattern, pulse rate, blood pressure, and blood glucose concentration, and mobile applications to provide feedback and motivate behavioural changes, have increased rapidly with growing penetration of mobile phone use globally. Other studies have shown that mobile technology can aid empowerment; enhance adherence to prescriptions; and encourage behavioural changes, such as improving healthy dietary habits, encouraging physical activity, and losing weight.[356]

Although these results support the potential of digital health solutions in increasing the reach and impact of lifestyle interventions and weight management programmes, health-care workers and professionals are often needed to improve engagement, suggesting that a so-called high technology, soft touch approach might address the psychosocial and informational needs of these individuals.[348] Similar to drug development, there are investment costs for developing, marketing, and maintaining these technologies with return of investment as a key consideration. Therefore, until there is sufficient evidence supported by cost-effectiveness analyses, sustainable engagement of health-care providers and patients' willingness to pay are major challenges in the scaling up of these prevention programmes.

More data-driven and context-relevant detection and prevention programmes are needed in LMICs

In a randomised controlled trial setting, individual-level lifestyle interventions aimed at changing obesity, diet, and physical activity had a generally similar effect in all populations and in all ethnic subgroups within populations.[357] However, these observations might be obscured by the dominance of participants from HICs. Compared with white populations, Asians have a lower acute insulin response for the same decrement in insulin sensitivity.[111,358] Within these populations, a small increase in adiposity, especially centrally, can worsen insulin resistance and decompensate β-cell function. Although weight reduction in these individuals at high risk might reduce risk of diabetes, alternative strategies targeted at ameliorating glucotoxicity to preserve β-cell function, especially in lean individuals with glucose intolerance, needs further exploration.[91] Approximately half of all individuals in randomised controlled trials on type 2 diabetes prevention are from Europe and the USA. The other half of participants are from India, China, and Japan (table 4). Without representative data from other regions, it is difficult to extend the cost-effectiveness of interventions on prevention of type 2 diabetes from HICs to LMICs, where data are scarce.[292] Besides, given the scarcity of information on other population-based risk factors and population attributable risks due to societal determinants, notably poverty and education,[153] maternal nutrition, early life stunting,[359] infections of various kinds,[360] dietary factors, and environmental factors (eg, pollutants), which are all highly prevalent in LMICs,[361] the cost-effectiveness of these lifestyle intervention programmes is uncertain.

For more on **these approaches from the Indian Ministry of Health and Family Welfare** see https://mohfw.gov.in

From effectiveness to efficiency of programmes for type 2 diabetes detection and prevention

Nearly all trials on type 2 diabetes prevention have focused on interventions in individuals with impaired glucose tolerance. However, in real-world practice, the 75 g oral glucose tolerance test is rarely used to detect abnormal glucose tolerance (ie, impaired fasting glucose, impaired glucose tolerance, or both) and few individuals measure their blood glucose concentration 2 h after the

challenge, which is needed to diagnose impaired glucose tolerance. Although there is epidemiological evidence suggesting that HbA_{1c} predicts incident diabetes and cardiovascular disease in a non-diabetic population in a linear manner,[362,363] there is scarce evidence regarding the benefits of prevention programmes for type 2 diabetes among individuals with isolated impaired fasting glucose or with isolated and elevated HbA_{1c}.[364] There are also gaps in knowledge regarding the effects of haemoglobin variants[365] and thresholds for haemoglobin glycation, which can influence the diagnostic values of HbA_{1c} in different ethnic groups.[366,367]

Additionally, regardless of the definition used, hyperglycaemia per se might not be the best way to target individuals at high risk. Instead, its combination with other information into a risk score is more robust in predicting risk of diabetes.[368] These risk factors can be based on questionnaires (eg, family history of diabetes, use of tobacco, history of maternal hyperglycaemia, hypertension, high blood cholesterol concentration, non-alcoholic fatty liver disease, polycystic ovary syndrome, or a combination of all factors) and self-measurement (eg, blood pressure, BMI, waist circumference) for incorporation into various risk scores to detect individuals at high risk of diabetes suitable for intervention. There are now many published risk scores that require validation and calibration when applied to different populations.[369] These unanswered questions, aimed at identifying individuals who will benefit most from lifestyle interventions, require further research and evaluation to assist decision makers in delivering interventions in the most efficient and cost-effective manner.

Pharmacotherapy, such as low-cost metformin, might have a place either as an alternative or as an adjunct intervention.[350] However, pharmacological prevention of type 2 diabetes implies that an individual will receive a diagnosis and glucose-lowering therapy, and attend a physician regularly for monitoring. Given the great number of people at risk, intervention with medical procedures and medications; for example, metformin, which is at best effective in only 10–15% of people with impaired glucose tolerance, should not be considered without a high level of certainty. Nevertheless, given the effectiveness of lifestyle intervention and metformin in individuals at high risk of conversion or in patients with practical difficulties in adhering to structured lifestyle intervention, a combination of metformin and lifestyle intervention, or early use of metformin as an alternative to lifestyle intervention, are options worth exploring.

One of the limitations in these trials is the proxy endpoints, because the goal of preventing type 2 diabetes is not only to reduce its incidence but also to reduce its clinical complications.[370,371] Because cardiovascular disease is the leading cause of death in patients with diabetes or abnormal glucose regulation, there is also a strong argument for use of a polypill strategy. This approach involves a fixed dose of several inexpensive medications that might prevent type 2 diabetes and cardiovascular disease, such as metformin, statins, and renin–angiotensin system inhibitors, and

	Studies	Number of incident cases	Relative risk estimate
Behavioural			
Smith et al, 2016			
Overall physical activity	28 cohorts: 12 from North America, eight from Europe, six from Asia, and two from Australasia	84 134	0·87 per 10 MET h/week difference in physical activity
Wilmot et al, 2012			
Sedentary behaviour	Nine cohorts: five from North America, two from Europe, and two from Australasia	23 230	2·12 comparing highest level of sedentary behaviour with lowest level
Zaccardi et al, 2015			
Fitness-enhancing physical activity	Seven cohorts: four from North America, two from Asia, and one from Europe	8564	0·95 per 1 MET higher than baseline cardiorespiratory fitness
Shan et al, 2015			
Sleep	Ten cohorts: five from North America, two from Europe, two from Asia, one from Australasia	18 443	U shaped relationship with lowest risk at sleep duration of 7–8 h/day
Jannasch et al, 2017			
Dietary patterns (ie, Mediterranean diet, dietary approaches to stop hypertension, alternative healthy eating index)	16 cohorts	Not specified	Between extreme quantiles; Mediterranean diet 0·87; dietary approaches to stop hypertension 0·81; alternative healthy eating index 0·79
Micha et al, 2017			
Nuts or seeds	Five cohorts	13 308	0·87 per 4 servings per week
Whole grains	Ten cohorts	19 791	0·88 per 1 serving per day
Red meat	Nine cohorts	28 228	1·19 per 1 serving per day
Processed meat	Eight cohort	26 256	1·51 per 1 serving per day
Yoghurt	Nine cohorts	32 995	0·82 per 1 serving per day
Sugar-sweetened beverages	17 cohorts	38 253	1·27 per 1 serving per day
Fibre	Five cohorts	3029	0·76 per 30 g/day
Glycaemic load	17 cohorts	46 115	1·13 high load *vs* low load
de Souza et al, 2015			
Macronutrients (eg, saturated fat)	Eight cohorts: four from Europe, four from North America	8739	0·95; non-significant association
Song et al, 2013			
Micronutrients (eg, vitamin D)	21 cohorts	4996	0·62 high serum 25(OH)D levels *vs* low serum 25(OH)D levels
Pan et al, 2015			
Smoking	88 cohorts	295 446	1·37 current smokers *vs* non-smokers (never smoked)
Knott et al, 2015			
Alcohol	38 cohorts: 11 from North America, 11 from Europe, 12 from Asia, and four from Australasia	125 926	0·82 in individuals consuming 10–14 g/day *vs* abstainers

(Table 4 continues on next page)

should be a key priority for governments and other sponsors, including the pharmaceutical industry.[372] Several randomised controlled trials have shown the effectiveness of polypills in improving the control of multiple risk factors, including blood pressure and lipids, in LMICs and HICs.[373–375] In a 5 year randomised controlled trial in Iran, involving patients (aged 40–75 years) with cardiovascular disease, cardiometabolic risk factors, or both, treatment with a four-in-one pill (hydrochlorothiazide 12·5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg) reduced risk of cardiovascular disease by 20–40%, depending on history of cardiovascular disease, with overall good safety and adherence.[376]

Short-term and long-term effects of primary prevention of type 2 diabetes on health-care use

The decision to introduce systematic screening for patients with undiagnosed diabetes in many settings has been guided by WHO's criteria for screening programmes.[377–379] Screening for undiagnosed diabetes fulfils many of the classical screening criteria, namely high prevalence, a long detectable preclinical phase, reliable screening method, and effective intervention. Modelling studies suggest that screening brings forward the point of diabetes diagnosis by approximately 3 years. Based on data from the ADDITION-Europe cohort, researchers simulated models indicating that screening followed by multifactorial management resulted in 3·3% absolute risk reduction and 29% relative risk reduction at 3 years, and 4·9% absolute risk reduction and 38% relative risk reduction at 6 years for cardiovascular disease.[380] Although long-term observational data from the ADDITION cohort is yet to support the benefits of screening on cardiovascular disease or all-cause mortality,[381] a health economic analysis from Denmark reported lower health-care costs in the group screened for diabetes than in the non-screened group, with the screening programme saving costs among individuals who screened positive for diabetes.[382] A mathematical modelling exercise has suggested that in the US population, screening for type 2 diabetes would be cost-effective when started between the age of 30 years and 45 years, with screening repeated every 3–5 years.[383]

Most experts recommend a screening strategy targeted at individuals at high risk who present with risk factors and risk markers for the disease, such as obesity and high blood pressure, which can be self-assessed. These data can be used to compute risk scores to detect individuals at high risk, followed by confirmatory laboratory tests including 75 g oral glucose tolerance test, HbA_{1c}, or both.[369] Regarding the best lifestyle intervention strategy, systematic reviews (including economic analyses) suggest that promoting healthy diet and physical activity, especially if delivered in groups or in primary care settings, and targeting individuals at high risk can be cost-effective in LMICs and HICs.[348,349,384]

	Studies	Number of incident cases	Relative risk estimate
(Continued from previous page)			
Social			
Sui et al, 2016			
Work-related stress	Seven cohorts: two from North America, four from Europe, and one from Asia	5511	1·12 job strain *vs* no job strain; non-significant association
Knol et al, 2006			
Depression	Nine cohorts: six from North America, two from Europe; and one from Asia	Not specified	1·37 depression *vs* no depression
Agardh et al, 2011			
Education	23 cohorts: ten from North America, seven from Europe, two from Asia, one from the Middle East, one from Latin America, and two from Africa	21 978	1·41 high educational attainment *vs* low educational attainment
Environmental			
Eze et al, 2015			
Air pollution	Five cohorts: three from North America and two from Europe	Not specified	1·10 per 10 μg/m³ particulate matter ≤2·5 μm in diameter
Song et al, 2016			
Food contaminants	Eight cohorts	Not specified	Highest concentration *vs* lowest concentration: 1·91 dioxin; 2·39 total polychlorinated biphenyls; 2·30 chlorinated pesticides
Developmental			
Mi et al, 2017			
Birth weight	Eight cohorts: three from North America, four from Europe, and one from Asia	3892	1·55 low birthweight (<2500 g) *vs* normal birthweight
Horta et al, 2015			
Breastfeeding	11 cohorts: not specified	Not specified	0·65 breastfeeding *vs* not breastfeeding
Janghorlani et al, 2014			
Age at puberty	Ten studies: three from Europe, five from North America, and two from Asia	22 085	1·22 low age at menarche *vs* average age at menarche

For the full references in this table, see the appendix p 14. MET=metabolic equivalent of task.

Table 4: **Summary of evidence of modifiable risk factors and their associated risk in type 2 diabetes**

In LMICs that can least afford to pay for expensive and late-stage complications, there is a strong economic argument to screen individuals at high risk of diabetes for lifestyle intervention. However, this strategy will undoubtedly lead to identification of many individuals with previously undiagnosed diabetes, which can be as high as 70% in some LMICs.[385] In a nationwide screening programme done in Brazil, individuals aged 40 years or older were invited to undergo capillary blood glucose testing at primary health-care centres through mass media and an awareness campaign. Individuals with a positive test were recalled to have a confirmatory test by use of fasting plasma glucose concentration. The programme aimed to detect undiagnosed diabetes and

to build capacity of primary care teams. Among 22 069 905 screening tests performed, 3 417 106 (15·5%) were screened positive. Among these positive results, 346 168 (10·1%) were confirmed as new cases and 319 157 (92·2%) were incorporated into the health-care system.[386]

The uncovering of this large population with undiagnosed diabetes who need continuing care, assessment, education, and medications have huge resource implications, which might compromise the care of individuals diagnosed through standard clinical channels and could result in competition for the resources needed for primary prevention by lifestyle intervention. Even for programmes aimed at detecting and treating HIV infections, supported by philanthropic funds, there are still persistent gaps in achieving targets.[387] Thus, the implementation of resource-efficient prevention programmes for type 2 diabetes on a large scale, targeting individuals at high risk and detecting and treating undiagnosed diabetes, should be supported by a prepared health-care system.[388,389] In LMICs, this system will need upfront investments in building infrastructures and capacity.[390] To maximise use of finite resources, intersectoral collaborations and public–private partnership are needed to develop an integrated system with physicians and non-physician personnel covering the full spectrum of health promotion, prevention, treatment, and rehabilitation. Furthermore, these individual-level efforts need to be paired with effective population-level efforts to maximally influence the trajectory of the type 2 diabetes epidemic, tailored according to each country's environmental and political contexts.

Population-level and individual-level prevention: balancing and evaluating

Risk factors that are the targets of effective individual-level interventions (eg, lifestyle interventions) should also be targets for population-level interventions,[391] although adoption of a population-based approach calls for improved understanding of the key determinants of environmental and behavioural drivers of type 2 diabetes risk, relevant to the area concerned. Physical activity, dietary behaviour, and obesity are often seen as an individual's choice or preference. However, these behaviours and social norms are driven principally by upstream, society-level factors, such as overall food supply, price, and marketing; the sedentary nature of most modern occupations; the scarce availability of health-promoting transport options; and the structure of the built environment. From this perspective, the emergence of type 2 diabetes is predominantly a societal problem for which society-level solutions are also required.[392]

The evidence of association and population attributable risk is less clear for a range of social, developmental, environmental, and behavioural risk factors than for individual-level factors (table 4). The extent to which these risk factors could be modified and form the target of future preventive interventions has not been adequately studied. Ideally, all important decisions should be based on evidence supported by facts and figures. In the case of health-related issues, a linear approach is often adopted in which interventions are developed, usually with a randomised controlled trial design, and tested in multiple populations and settings. When the intervention is found to be effective, meta-analyses and systematic reviews of similar results follow, which contribute to the formulation of practice guidelines informed by evidence and public policies, as is the case for management and prevention of type 2 diabetes in individuals at high risk.[393]

There are a few examples of population-level interventions, in which researchers used randomised controlled trials to show the effects of salt substitution on reducing blood pressure,[394] and those of housing vouchers and counselling on encouraging women and their children to move from areas of high poverty to those of low poverty, which have reduced prevalence of extreme obesity and diabetes.[395] Although this reductionist randomised controlled trial approach follows classical teaching, given the public health threat posed by type 2 diabetes, bold policy-level action followed by evaluation by a range of quasi-experimental methods is an alternative approach (figure 10).[396] In this fundamentally different approach, best available observational evidence is used to support a policy-level intervention, which is then evaluated in real-world settings by use of quasi-experimental methods. Measures to cut tobacco use[340] to reduce deaths, and mandatory seat belt use to reduce road traffic injury have followed this approach.[397]

In Scotland, a policy intervention that prohibited smoking in all enclosed public places was enacted in 2006. Only after this policy was put in place was it possible to evaluate its effects on ischaemic heart disease. Compared with the number of admissions due to acute coronary syndrome in the 10 month period before the passing of the legislation, there was a 17% reduction during the same period in the year following its enactment.[398] When similar interventions have been implemented elsewhere, evidence synthesis of the effectiveness of tobacco control strategies was then possible by use of meta-analysis.[399] Given the multidimensional nature of diabetes, multiple society-level interventions will be required, albeit each one might only have a small effect. For example, policies to implement sugar-sweetened beverage taxes and levies are being increasingly evaluated;[400] however, such evaluations are usually focused on proximal outcomes, such as purchasing or consumption. In this type of policy intervention, distant outcomes (eg, incidence of type 2 diabetes) have to be modelled rather than directly observed.[401]

Primary prevention of type 2 diabetes requires bold, evidence-informed political actions

Recognising the life-course of diabetes and other NCDs, members of this Commission reiterate the importance of applying educational policy at all levels (including,

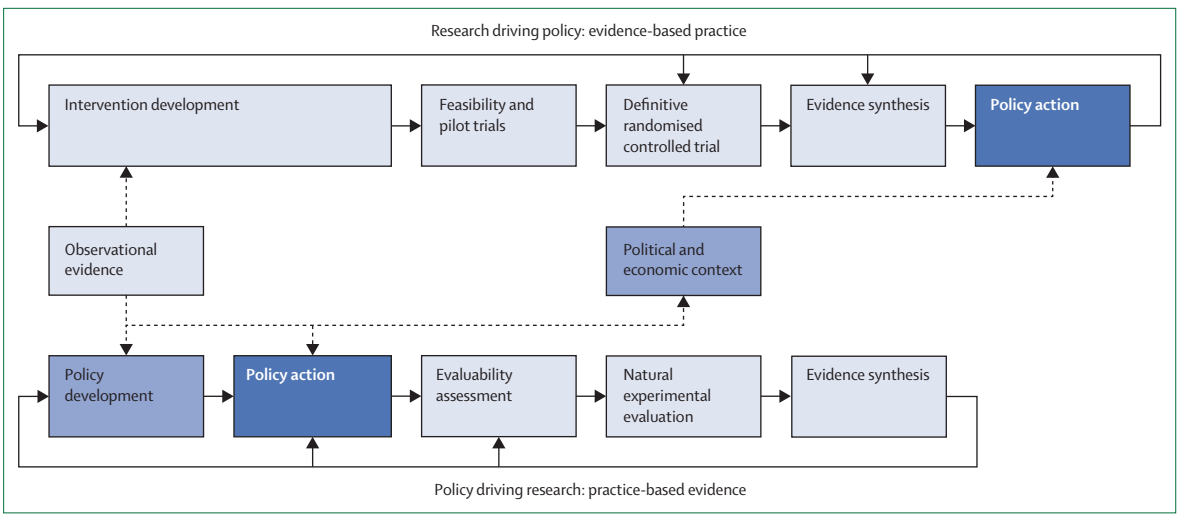

Figure 10: **Routes to the translation of evidence into action in clinical and public health interventions**
Reproduced from Ogilvie et al,[396] by permission of British Medical Journal Group.

but not limited to, preschool, school, college, and university) to improve literacy, self-management, and lifelong coping skills as an overriding strategy to promote health and prevent disease. Members also emphasise the importance of environmental policies in building healthy cities through intersectoral collaborations with clean air, water, and foods to protect health and reduce harm. Given the importance of ischaemic heart disease and cancer as the leading causes of morbidity in type 2 diabetes, members also reaffirm the importance of tobacco control as an important policy in the prevention of this type of diabetes and its complications. These societal strategies accord with WHO's *Best Buys*[330,340] and the recommendations by the UN SDGs.[339]

Within this framework, members of this Commission further proposed a series of possible actions that could be implemented by governments and policy makers at the supranational, national, regional, and local levels to influence risk factors (table 3). The approach used in any given setting will be determined by not only epidemiological considerations of expected benefit but also those of political feasibility. The cost-effectiveness of some of these population-level interventions have been evaluated, including sugar-sweetened beverage taxes,[402] restrictions on unhealthy food advertising,[403] mass media campaigns to promote healthy lifestyle,[404] and economic incentives to increase fruit and vegetable consumption.[405,406]

Because the effectiveness of such interventions cannot be determined from randomised controlled trials, simulation modelling is often used to estimate their cost-effectiveness. Evidence from the few studies available suggests that these interventions are generally cost saving or cost-effective.[407] Studies of the cost-effectiveness of fruit and vegetable subsidies were inconclusive. Naturally, such interventions are usually considerably less effective than targeted individual-level interventions, but because the effect is amassed across the whole population, they can result in a large aggregate health benefit. Because these interventions are relatively inexpensive, they can be cost-effective, albeit with wide limits of uncertainty. Population-targeted interventions also carry logistic and political challenges and sometimes the risk of unintended consequences, such as behavioural substitution effects. Because estimates of cost and effectiveness of population-wide interventions have been modelled up from numerous assumptions, rigorous natural experiments are needed to evaluate effectiveness and to help the prioritisation and implementation of such approaches.

Decisions to allocate resources for screening, prevention, and treatment are often context-relevant, considering local cultures, socioeconomic development, and existing capacity of health-care systems. Nevertheless, given the life-threatening nature of untreated or poorly managed diabetes, it is important that all health-care settings act promptly to provide care, meeting minimal standards for all individuals diagnosed with diabetes. People who are in contact with health-care settings and have a high likelihood of having prevalent but undiagnosed diabetes should have a diagnostic test and, if positive, should be included in the same system of care as those people with known diabetes. The implementation of systematic approaches to find individuals with undiagnosed diabetes and patients at high risk of future diabetes is a contextual health-care policy decision, influenced by the structure of individual health-care systems.

An example to illustrate priority actions in HICs versus LMICs

Depending on the environmental, political, and social context, policy makers will need to adopt a multi-component strategy to combine population-wide and

individual-level interventions aimed at individuals at high risk. Most scientific literature suggests that obesity, physical inactivity, and different dietary and nutritional factors are among the most modifiable risk factors, which form the basis of many individual-level primary prevention programmes. With the USA as an example, the population attributable risk due to obesity, poor diet, and physical inactivity was 87% among women, suggesting that most cases of type 2 diabetes could be averted if women adopted a healthy diet, were physically active, and did not have obesity.[408] However, the dominance of North American and European populations in the literature on risk factors and risk of type 2 diabetes (table 4), and the scarce data from Asian and African populations raise the question about whether or not estimates of population attributable risk could differ between populations. Accordingly, local data regarding population attributable risk due to risk factors (eg, access to healthy food choices, food insecurity, nutrition, sleep pattern, physical activity, and psychosocial stress), considering demographic, environmental, and socioeconomic determinants, become important for prioritising actions.

	Jamaica[409]	England[410]
Country demographics and health care		
Total adult population (1000s)	2881	65 640
GDP per capita, purchasing power parity (current international $)	8835	42 609
Total health-care expenditure of GDP % per capita (US$)	5·4% GDP per capita ($266)	9·1% GDP per capita ($3935)
General government health-care expenditure (% of total health expenditure)	52%	83%
Density of physicians (total number per 1000 population)	0·4	2·8
Density of nursing and midwifery personnel (total number per 1000 population)	1·1	8·4
Current burden of disease		
Prevalence of diabetes in women, %	14·4% (7·8–23·3)	4·9% (3·1–7·4)
Prevalence of diabetes in men, %	9·3% (4·5–16·0)	6·6% (4·1–9·7)
Prevalence of non-diabetic hyperglycaemia, %	2·8%	10·7%
Proportion of diabetes undiagnosed, %	23·9%	2·3%
Future burden of disease		
Estimated prevalence of diabetes in women in 2025, %	21·6% (7·2–49·8)	5·4% (2·1–11·6)
Estimated prevalence of diabetes in men in 2025, %	13·7% (3·7–33·8)	7·8% (3·1–15·9)
Current prevalence of risk factors		
Prevalence of high blood pressure in women, %	19·2% (12·0–27·7)	12·4% (9·0–16·1)
Prevalence of high blood pressure in men, %	24·5% (15·6–34·8)	17·9% (13·0–23·2)
Prevalence of overweight and obesity in women, %	63·4% (56·5–70·0)	58·5% (53·8–63·0)
Prevalence of overweight and obesity in men, %	48·3% (41·0–55·4)	67·7% (63·3–72·0)
Prevalence of obesity in women, %	33·0% (25·7–40·0)	28·3% (24·2–32·5)
Prevalence of obesity in men, %	15·2% (10·0–21·2)	26·2% (22·1–30·5)
Future prevalence of risk factors		
Estimated prevalence of obesity in women in 2025, %	43·2% (29·5–59·1)	37·6% (28·7–47·7)
Estimated prevalence of obesity in men in 2025, %	25·7% (13·2–43·6)	37·8% (27·7–49·9)
Quality of diabetes care		
People with diabetes with HbA_{1c} or fasting blood glucose concentration within target range, %	43·0%	65·7%
People with diabetes with lipid concentration under control, %	No population-based data	77·1%
People with diabetes with blood pressure <140/90 mm Hg, %	16–94%	73·6%
Diabetes register?	Yes	Yes

(Table 5 continues on next page)

The balance between prevention approaches in individuals at high risk on an individual-level and on a society-level might differ between countries and even within a country over time. Countries should consider the scale of the diabetes problem in their own populations, the ratio of diagnosed to undiagnosed cases, and the capacity of primary health-care systems to offer screening for undiagnosed diabetes and hyperglycaemia, to care adequately for additional cases, and to provide systematic preventive interventions for individuals at risk.

England has a relatively low prevalence of diabetes, and the proportion of undiagnosed cases has fallen over the past 20 years, probably due to improved case finding (table 5). The country has a strong and well funded primary health-care system, with most patients with diabetes having access to regular screening for complications and medications for controlling risk factors. Such a system can cope with the establishment of a wide-scale effort to implement a screening and lifestyle intervention programme for type 2 diabetes that will complement population-wide prevention strategies.

By contrast, funding in Jamaica is far lower than in England (table 5) and many individuals with diabetes do not have access to screening for complications or risk factor control. In this resource-limited setting, changing the health-care system to improve diabetes care for the existing population is a priority.[409] Although it might seem intuitive to encourage investment in screening for individuals at high risk in individual-level interventions, this would risk destabilising an already stretched health-care system. Given the scale of the problem, in addition to improving care standards and patient education by use of non-physician personnel and ensuring access to essential medications, it might be preferable to give even greater priority to interventions aimed at shifting risk factors in the whole population. For example, Caribbean countries have taxed sugar and are currently implementing other fiscal measures. This contrast between England and Jamaica illustrates the need for countries to individually consider a range of epidemiological, economic, and health-care system factors when determining the appropriate balance between investments in improving the health care of individuals who currently have diabetes, interventions in people who will have the disease in the future, and upstream changes that have the potential to influence risk of diabetes in future generations.

An epidemic requires local solutions through collective efforts

We are living in a rapidly changing society where globalisation and technological advancement have increased life expectancy in many parts of the world. These forces have created big changes to our social, physical, and food environment, and together with increasing communication of information and goods, there are also changes in our cultures and value systems. Given the social nature of human beings subjected to external pressure and peer influence, these societal changes have transformed our perspectives, expectations, and behaviours, leading to new social norms (notably, lifestyles associated with city dwelling). Rapid rural–urban migration has led to progressive widening of social disparities and increasing income inequality, partly driven by pressure to maximise profits and outputs. These multidimensional changes have made diabetes not only a medical but also a social and political challenge.

The COVID-19 pandemic has been a wake-up call to the global community on how patients with diabetes and NCDs, especially individuals with poor access to care and social deprivation, are disproportionately affected during these emergencies. The large number of people affected by COVID-19 overwhelmed the health-care system, even in HICs, with considerable human suffering and economic repercussions.[411–414] In this light, most health-care systems in LMICs are traditionally designed to treat acute injuries and communicable disease. Not only are these resource-limited systems unable to cope with these global emergencies, but they are also ill prepared to manage this growing number of individuals with diabetes and their long-term complications. Despite the rapid knowledge and technological advancement in diabetes and other NCDs, the rudimentary primary care systems and insufficient training of health-care providers mean that many individuals are not diagnosed, treated, or controlled in a timely manner.

Even in affluent areas in HICs, decades of social and medical care consumed by the growing population of people with diabetes is having a substantial toll on their well resourced health-care systems. Many decision makers have little information to plan resource allocations for designing, developing, and sustaining a high-quality and integrated prevention and care service with long-term benefits for patients with diabetes. The sheer number of individuals with or at risk of diabetes also deters many payers (including insurers, governments, and corporates) to invest and opt for status quo,[415] despite the cost-effective or cost saving nature of these prevention and care programmes.[416] Aside from improving care, strong political will and intersectoral collaborations are needed to tackle many of these societal determinants closely linked with diabetes, notably environment, education, and poverty.

	Jamaica[409]	England[410]
(Continued from previous page)		
Screening for diabetic complications		
People with diabetes who have annual diabetic retinopathy screening, %	No population-based data	82·5%
People with diabetes who have annual foot risk surveillance, %	No population-based data	86·7%
Current available treatments		
Insulin available in the public sector?	Yes	Yes
Metformin available in the public sector?	Yes	Yes
Statins available in the public sector?	Yes	Yes
Current policy		
Operational policy–strategy–action plan for diabetes?	Yes	Yes
Operational policy–strategy–action plan for reducing physical inactivity?	Yes	Yes
Operational diabetes policy–strategy–action plan for reducing unhealthy diet?	Yes	Yes
Screening available?	No	First wave of NHS Diabetes Prevention Programme covering 26 million people in 2016

Prevalence data expressed as % (95% CI). GDP=gross domestic product. HbA_{1c}=glycated haemoglobin A_{1c}. NHS=National Health Service.

Table 5: **Differences between Jamaica and England in demographic and organisational factors influencing policies for prevention of type 2 diabetes**

An integrated society–population–community strategy to reduce burden of diabetes and other NCDs

Given the multidimensional nature of diabetes, a multidimensional solution is needed to create short-term, mid-term, and long-term impacts. In this Commission, we have reviewed and curated a large body of evidence supporting the environment–host–lifestyle interactions in unmasking diabetes in predisposed individuals. When diabetes develops, care fragmentation and insufficient patient engagement can worsen control of multiple risk factors, leading to multiple morbidities. Due to the silent nature, phenotypic heterogeneity, and pluralistic needs of diabetes, we argue strongly for the need to redesign the practice environment, team structure, and workflow to gather data systematically, stratify risk, personalise care, provide feedback, and perform periodic monitoring. By establishing community-based diabetes teams or centres and by building a strong primary health-care system with linkage to hospital-based health-care systems, trained diabetes teams will be in a prime position to identify individuals at high risk for lifestyle interventions, including the use of metformin and other medications (eg, polypill), to prevent type 2 diabetes and cardiovascular disease.

This individualised approach needs to be complemented by policies that support building smoke-free, healthy cities aiming to reduce environmental pollutions, ensure food security, increase affordability of healthy foods, promote healthy eating (eg, nutritional labelling and school meals), encourage physical activity (eg, walking paths and sports), and avoid use of harmful

For more on the **Cities Changing Diabetes programme** see http://www.citieschangingdiabetes.com

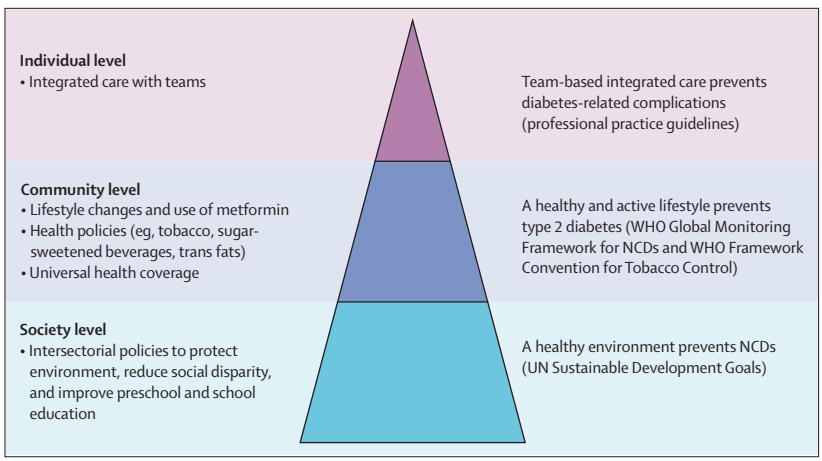

Figure 11: **A conceptual framework for a multicomponent society–community–individual strategy to integrate primary and secondary prevention of type 2 diabetes**
This strategy is supported by health and intersectoral policies in line with the UN Sustainable Development Goals, WHO NCD Global Monitoring Framework, WHO Framework Convention for Tobacco Control, and professional practice guidelines. NCD=non-communicable disease.

substances (eg, tobacco, sugar-sweetened beverages, trans fats) by use of taxation and warning labels. To reduce the long-term burden of diabetes and other NCDs, policy makers and planners need to use intersectoral polices to improve the ecosystem, protect the environment, and reduce social disparities. Apart from promoting universal health coverage, providing education from preschool level to at least secondary school level will help to improve literacy closely linked to improved health awareness and disease prevention (figure 11).

Interventions directed at health-care systems and patients with diabetes

The differences in clinical outcomes between ethnicities, such as high rates of diabetic kidney disease reported in Asian populations compared with white populations in epidemiological surveys,[417] were considerably attenuated in randomised controlled trial settings where access to care and support was assured and structured.[217,418] Compared with young and newly diagnosed patients in the UKPDS, which was done in the era before statins and renin–angiotensin system inhibitors were used,[263,264] participants with either cardiovascular disease or multiple risk factors in landmark studies, including the ACCORD,[230] VADT,[231] and ADVANCE trials,[232] had 50% lower incidence of cardiovascular events and death.[419] In the Steno-2 study[420] and J-DOIT3 study,[421] in which patients received intensive treatment to control multiple risk factors, there were marked reductions in cardiovascular–renal events and death rates.[422]

For example, the J-DOIT3 study recruited 2540 Japanese patients (aged 45–69 years), of whom 288 individuals (11%) had a history of cardiovascular disease. Patients randomly assigned to the group receiving intensive treatment were informed of their treatment targets and were given equipment to monitor their blood pressure and blood glucose concentration at home with access to nurse education, while their attending physicians were asked to reduce their risk factors within 6 months. This multicomponent strategy led to a total of 109 events (9%), with no end-stage kidney disease events and fewer than 100 cardiovascular events at 8 years. These examples show how the delivery of structured and continuing care by use of a team approach with regular monitoring and access to life-saving medications (eg, statins and renin–angiotensin system inhibitors), can lead to a great reduction in clinical events and death rates compared with those observed in usual care settings.[421,422]

Closing knowledge gaps in patient-important outcomes to improve psychological health and behaviours

Although randomised controlled trials and meta-analyses have supported the benefits of reducing multiple risk factors in improving clinical outcomes,[209,211,212] the volunteer bias of participants and investigators, and the artificial nature of trial settings, pose major challenges in translation, partly due to poor access, affordability, and adherence. Few randomised controlled trials reported patient-important outcomes, such as quality of life, treatment costs (direct or indirect), and use of hospitalisation resources as primary outcomes.[423] Compared with the many randomised controlled trials evaluating technologies, few research studies have examined the societal–economical–cultural factors that underlie behavioural changes to establish positive outcomes. When available, these studies often yielded inconsistent results with poorly defined constructs, evaluation processes, and outcomes.

In most practice guidelines for management of complex conditions (including diabetes), lack of consideration of patients' societal–personal context, personal values, and preferences have reduced their relevance and effective implementation, especially in LMICs or resource-limited settings.[424,425] In some populations that are vulnerable due to social inequalities or cultural barriers, use of outreach programmes or community-based centres might improve access to care compared with traditional settings based in clinics or hospitals. Similarly, use of trained, non-physician personnel (eg, trained community health workers or peers) to empower and support these individuals and their families to manage stress and solve problems during their day-to-day lives with diabetes might enhance patients' resilience in self-management.[426]

To translate these efficacy data in trial settings to cost-effectiveness data in real-world practice, policy makers and planners need to develop frameworks in which environment, care settings, providers, processes, supporting systems, and payers are aligned to create impact.[427] To close these knowledge gaps, investment is required to fund new research methods and studies in real-world settings, with publications of these results in

leading academic journals to create a framework shift focusing on implementation and evaluation in these settings.[428]

Developing diabetes as a specialty subject to improve standards, build capacity, and establish diabetes teams

Many governments have pledged to provide universal health coverage, including essential medicines as outlined in the UN SDGs and WHO NCD Global Monitoring Framework. However, a coordinated system is needed to diagnose these patients, assess their clinical needs, prescribe medications, and ensure patient adherence to establish positive outcomes. By use of the physician per inhabitant ratio as an index of capacity, in 2018 the figures ranged between 5·0 per 1000 people in Cuba, 3·9 per 1000 people in Argentina, and 0·02 people per 1000 in Malawi. In the top three countries with the largest population of individuals with diabetes, the figures were 1·5 per 1000 people in China, 0·6 per 1000 people in India, and 2·3 per 1000 people in the USA. In Europe, the figures were 2·85 per 1000 people in the UK, 3·17 per 1000 people in France, and 3·99 per 1000 people in Italy. Even in countries or areas with ratios higher than that recommended by WHO of 1·9 per 1000 people,[429] there is a need to train non-physician personnel to assist physicians in providing continuing care of these individuals with multiple needs.

During the life journey of an individual with diabetes, the patient might need professional advice from specialists, family doctors, and allied health-care workers (eg, nurses, dietitians, social workers, pharmacists). Apart from friends and families, these individuals might need, yet frequently do not have, continuing support from trained community health workers or peers with well delineated roles to cope with the day-to-day challenges posed by self-management.[430] In many LMICs, knowledge transfer from skilled workers to community health workers and trained peers might be the only way to meet the huge service demands, pending health-care reforms and capacity building. In the Step by Step Foot Project piloted and completed in India and Tanzania, education of health-care providers and patients about proper limb care are used to reduce incidence of amputation.[431]

Although members of this Commission emphasise use of non-physician personnel to increase the accessibility and sustainability of diabetes care, given the large number of patients requiring diabetes care with different levels of complexity, and the shortage of health-care providers with special knowledge in diabetes (especially in LMICs), policy makers, payers, and planners are urged to increase investment and to develop diabetes as a specialty to improve care standards, provide training, and conduct research to inform practices and policies. Apart from building infrastructure, there is an urgent need to advance the career paths of health-care providers with appropriate knowledge and skills to reorganise care, develop teams, provide training on the job, and teach undergraduate students to close the gaps in professional knowledge as a prerequisite to delivering high-quality care for patients with diabetes.[432,433]

Use of a multicomponent strategy to implement evidence-based and patient-centred diabetes care

Implementation or improvement science refers to research methods aimed at understanding the determinants, processes, and effects of quality improvement. By promoting quality improvement as a science, health-care providers, planners, managers, payers, researchers, and system users (ie, people with the condition) can collectively design systems, train staff, and develop protocols to improve the quality of care with ongoing data collection to identify gaps in care and to evaluate effectiveness.[434] In Mexico, the implementation of a comprehensive programme to define risk profiles, individualise care, and empower patients resulted in considerable improvements in attaining HbA_{1c} targets and reducing negative emotions, although the proportion of patients who persisted with the programme decreased by more than 50% at 12 months and by more than 75% at 24 months.[435] In a meta-analysis of multicomponent quality improvement strategies targeting systems, patients, and health-care providers for 12 months or more, use of task shifting, patient education or self-management support, and facilitated relay (with nurses, health-care assistants, trained community health workers or colleagues, and information technologies) to improve patient–provider communication had the largest effect sizes in reducing HbA_{1c}, with similar improvements for blood pressure and LDL cholesterol concentration (figure 12).[276] Other meta-analyses also indicated that diabetes care models aimed at enhancing professional education and self-management improved treatment adherence, control of multiple risk factors, and clinical outcomes, and can be cost saving in patients with or without complications.[323,436,437]

Changing workflow and setting up diabetes registers to deliver data-driven care

In the 1990s, the International Diabetes Federation-Europe and WHO-Europe launched the St Vincent's Declaration, proposing structured data collection to detect microvascular complications (notably retinopathy and neuropathy) and to improve care standard in people with type 1 diabetes. This action was soon followed by a similar initiative in Latin America (ie, Diabetes Declaration of the Americas), in which a standardised form was adopted by many countries in the region to establish registers (ie, QUALIDIAB).[438] These initiatives provide useful information on how to use data from these registers to identify care gaps and monitor outcomes.[439] Many of these registers for type 1 diabetes, such as the Pittsburgh Diabetes Register (PA, USA) established in the early 1980s, have informed the world

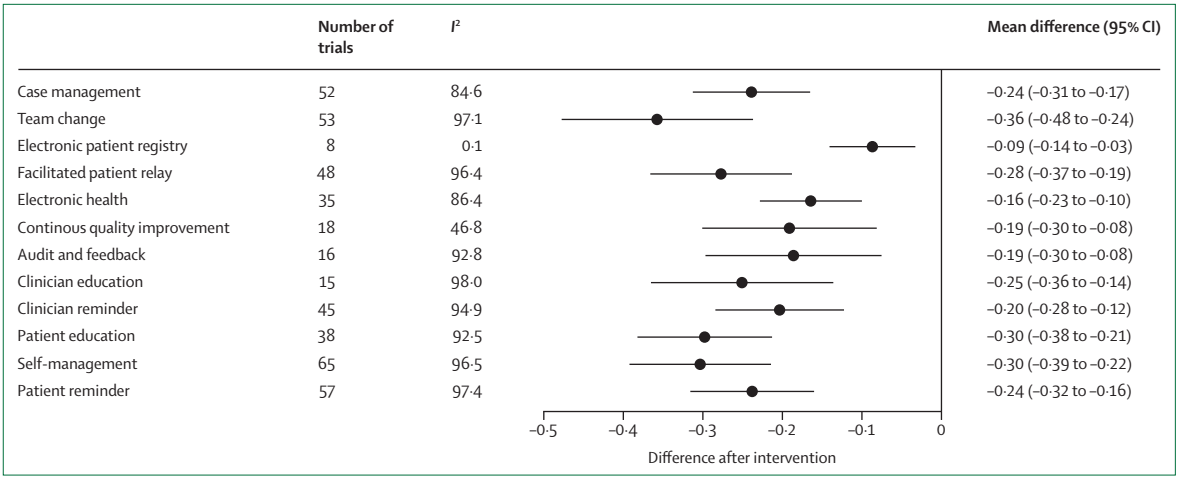

Figure 12: **Effects on HbA_{1c} of different quality improvement strategies targeted at patients, providers, and systems in patients with type 2 diabetes receiving multicomponent integrated care versus usual care**

Data taken from a meta-analysis of 181 trials involving 135 112 patients. Team change, facilitated patient relay, patient education, and self-management have the largest effect size, expressed as mean difference (95% CI). Similar changes are also reported for blood pressure and LDL cholesterol. Reproduced from Lim et al,[276] by permission of American Diabetes Association.

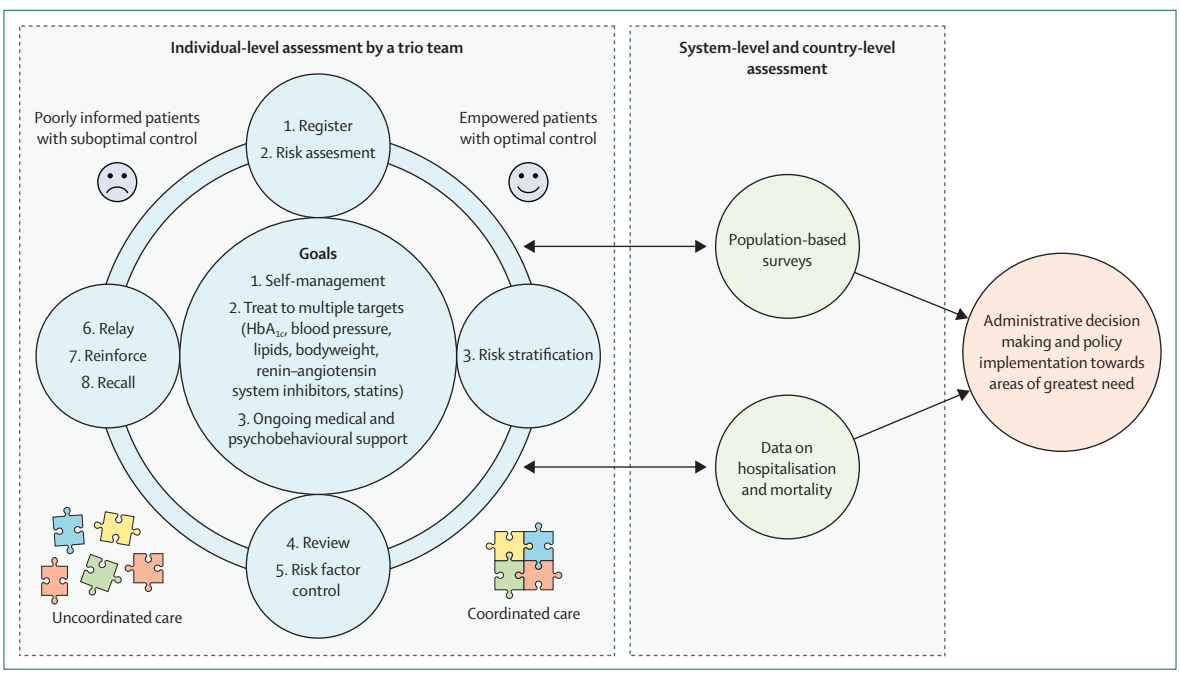

Figure 13: **Transforming fragmented diabetes care into integrated and data-driven diabetes care**

Use of a trio team (including trained nurses and health-care assistants, supervised by physicians) to systematically collect data during routine clinical practice can establish a register and apply data to empower self-management and treat to multiple targets with ongoing support. Data can be linked to population-based surveys, and hospitalisation and mortality data for audit and surveillance purposes to influence policies and practices. Reproduced from International Diabetes Foundation Diabetes Atlas,[5] by permission of International Diabetes Federation. HbA_{1c}=glycated haemoglobin A_{1c}.

about the marked variations in incidence and care standards, and about the secular trends of complications (figure 5).[440]

With the growing number of medications, most practice guidelines recommend periodic assessment of risk factors and comorbidities to individualise treatment targets and regimens.[239] To achieve these objectives, there is a need to establish a workflow to collect data systematically to stratify risk, triage care, and personalise management. When established, these diabetes registers can serve multiple purposes. On a patient level, data can be used to provide feedback and individualise care. On a system level, data can identify care gaps and benchmark performance. On a policy level, data can be linked to

population and hospitalisation data to identify root causes and to monitor disease patterns and burden (figure 13).[441]

Although not universally applicable, there are now institutional and national attempts to establish electronic medical record systems by digitalising patient-related information collected during routine practice. These data management systems are usually well designed and supported by good practices, including privacy protection. Depending on the complexity of the system, data types include demographics, hospitalisation, insurance claims, and medications. These electronic medical record systems can facilitate patient management of diabetes, such as the so-called pay for performance schemes in England[442] and Taiwan.[443] Other workers have designed simple databases and changed workflows to capture essential information during annual comprehensive assessment to set up diabetes registers for quality improvement. From a clinical perspective, when data are systematically collected, especially if relayed back to health-care providers, patients, and their caregivers, improvement in care standards often follows due to improved awareness and self-management, and intensified treatment with improved adherence.[444]

A step-by-step implementation plan to deliver a data-driven and integrated diabetes care plan

Many countries are now adopting WHO's recommendation of providing universal health coverage, including essential medicines (eg, metformin, sulfonylurea, insulin, statins, renin–angiotensin system inhibitors, aspirin). However, to ensure the appropriate and effective use of these medicines, health systems need to be strengthened with provision of regular assessment and education services to ensure timely diagnosis and intervention to avoid silent deterioration of risk factors and occurrence of complications.[445–448] Self-management, promoted by structured diabetes education, is the cornerstone of successful diabetes care.[261] In HICs, professional organisations have stipulated the credentials of educators and curriculum of diabetes self-management and education. In LMICs and resource-limited settings, trained physicians and nurses will need to take on trainer and manager roles to transfer knowledge, develop care protocols, design workflows, and train health-care assistants to take on these assessment and education tasks. Alternatively, doctors will need to focus on making clinical decisions, prescribing drugs, and looking after patients with complex problems. In HICs, improved care organisation with task shifting to facilitate team-based care can also lead to improved efficiency and affordability, decreasing patient default rates and increasing job satisfaction for the workforce.[449]

Based on care models that are already in operation in some areas, and in accordance with international guidelines,[239] members of this Commission have provided a template to help health-care providers, planners, and financers to initiate a structured and integrated assessment, education, and support programme (panel 1), which can be implemented even in resource-limited settings. These integrated services can be supervised by physicians but implemented by non-physician personnel, including nurses, health-care assistants, and trained college graduates, or patients with diabetes if nurses are in short supply (figure 13).[449,450] In the past decade, an increasing number of studies have shown the effectiveness of structured patient education and support programmes delivered by trained community health workers or colleagues in underserved communities across HICs and, to a lesser extent, across LMICs.[451–453] In a systematic review of 118 randomised programmes for education on diabetes self-management (defined as single and discrete interventions with one or more follow-up assessments of HbA_{1c} at a 3 month interval or longer), contact time of 10 h or more was associated with considerable HbA_{1c} reduction, compared with exposure of less than 10 h.[454] More than 12·0 months of this intervention was more likely to achieve considerable HbA_{1c} reduction than interventions that lasted for 2·5 months or less. The benefit was most evident in individuals with HbA_{1c} higher than 9·0% (75 mmol/mol), whereby intervention could lead to a reduction of HbA_{1c} by as much as 0·7% (7·7 mmol/mol), with more than 70% of patients showing considerable improvement.

Various facilities, equipment, and procedures are required to deliver an integrated assessment, education, and supporting service by a trained nurse–health-care assistant team, including the time scheduling of these sessions and the person-hours required for a unit of 800 patients (panel 2). A typical week can be divided into sessions in which non-physician personnel can be trained to gather clinical information, collect blood or urine samples, and perform eye (eg, visual acuity and fundus camera) or foot examinations (eg, sensation and pulses) to assess control of risk factors and detect complications. Depending on case complexity, a patient might need up to 1 h for a structured assessment at presentation and further assessments every 2–3 years thereafter for quality assurance. For newly diagnosed patients, an extended duration of education or contact time is recommended (eg, 10 h over 12 months in groups of ten patients).[454] The content should include nature of disease, treatment targets, regular follow-up and monitoring, healthy lifestyles, medication adherence, management of sick days, and other special issues (eg, planning for pregnancy or stress management). These group sessions can be followed by individualised sessions on the basis of the risk profiles and needs of the patient.[261,449] Given a total of 3840 person-hours of a nurse–health-care assistant team, members of this Commission estimated that 1600 person-hours can be used to perform structured assessment and 1200 person-hours for group education, with the remaining 1040 person-hours used to provide additional support as

For more on the **National Certification Board for Diabetes Educators** see http://www.ncbde.org

***Panel 2*: Delivery of a basic care plan for type 2 diabetes with a nurse–health-care assistant team in a diabetes centre to provide an integrated assessment, education, and supporting service aimed at complementing medical care and establishing a diabetes register for improving care standards**

Number of patients
- 800 patients depending on case mix

Workforce
- One nurse and one health-care assistant under medical supervision

Space
- 200–300 square feet with basic office equipment (eg, computer, email, telephone, fax, photocopying machines) for assessment and group education away from busy wards and clinics

Assessment tools
- Monofilament and tuning fork (ie, sensory neuropathy)
- Hand-held ophthalmoscope or fundus camera (ie, retinopathy)
- Blood tests (eg, plasma glucose concentration, HbA_{1c}, lipid concentration, renal and liver function, estimated glomerular filtration rate, uric acids, haematology)
- Urine tests (urinary albumin-to-creatinine ratio)

Education tools
- Charts and materials explaining nature of diabetes (eg, causes and consequences), plan of follow-up (eg, how often and by whom), self-monitoring (eg, nature and how often), lifestyle modification, use of medication, treatment targets (eg, HbA_{1c}, blood pressure, LDL cholesterol, bodyweight), sick day management, and demonstration of insulin pens and blood glucose monitoring devices

Assessment items
- Structured form for collection of age, sex, duration of diabetes, education, occupation, tobacco and alcohol intake, family history, self-care, feet (eg, skin, nerves, and blood vessels), and eye (eg, visual acuity, cataract, retinopathy, history of laser, or surgery), history of medical illness (notably hospitalisations due to ischaemic heart disease, stroke, cancer, lower extremity amputation), major operations or procedures, and clinically significant symptoms (eg, erectile dysfunction)

Computer database
- Data collection for audit and recall purpose
- Use of risk equations to estimate future risk of events with reports that are simple to read, and decision support depending on availability and support

Frequency of assessment
- Baseline assessment followed by assessment at 6–9 months with increased frequency of follow-up for education, reinforcement, and treatment adjustment
- Repeat assessment at 12 months to review progress and every 24–36 months thereafter, with 4–6 monthly review when stable

Other activities
- Group education, individual education, teaching of techniques, other classes on diet, physical activity, stress management, screening of family members and individuals at high risk (eg, polycystic ovary syndrome, gestational diabetes, family history), and peer support depending on availability of resources

For a workflow and the required person-hours of the nurse–health-care assistant team, see the appendix p 21. HbA_{1c}=glycated haemoglobin A_{1c}.

needed (panel 2; appendix p 21). After these patients are stabilised and educated, less contact time will be required and the team can then take on other tasks, such as detecting individuals who are at risk of or have undiagnosed diabetes for early intervention (eg, positive family history, obesity, history of gestational diabetes, polycystic ovary syndrome, hypertension, dyslipidaemia, non-alcoholic fatty liver disease, smoking, or high-risk scores).[369]

To maximise efficiency, clerical staff, health-care assistants, or both, can be trained to perform simple measurements (eg, blood pressure, bodyweight, body height, waist circumference), collect biosamples (eg, urine and blood), ask non-clinical questions (eg, demographic data or self-care), prepare record forms, enter data, generate reports, book appointments, recall patients, and manage the database. Clinical staff can concentrate on tasks such as data review, education, decision making, and treatment adjustments. Depending on availability, these care protocols can be incorporated within the institutional electronic medical records. Alternatively, these databases can stand alone and be periodically linked to other administrative databases for monitoring of outcomes. Even in areas without electronic medical records, personal computers can be used to digitalise these paper and pen registers to enable patient recall every 2–3 years to avoid default and to ascertain clinical outcomes, including death.

Importantly, these structured protocols for gathering data, together with continuing care by the same diabetes team and ongoing evaluation, can facilitate training on the job and motivate members to champion these evidence-based care models.[326,455] When these infrastructures and teams are put in place, culturally sensitive and specific programmes can be designed, such as peer support, home visits, outreach, and mobile health programmes to address the needs of different patient groups (eg, patients with young-onset diabetes, or who have obesity, multiple medications [including insulin injections], psychosocial stress, or poor adherence).[456] In some settings, notably in LMICs pending health-care investments and reforms, co-sharing of facilities and staff time for management of complex diseases (eg, tuberculosis or HIV infection) can initiate and expedite the formation of these diabetes teams to provide data-driven, integrated care for these diseases requiring long-term care.[170,457,458]

Due to the continuing nature of diabetes management, which encompasses prevention, diagnosis, treatment, and rehabilitation, and depends on health-care financing and workforce development in each region, these community-based diabetes teams with linkage to diabetes centres led by specialists should preferably have a predefined provider–patient ratio to avoid overuse or underuse of resources. On the basis of existing models, members of this Commission estimate that 0·25–0·50 physician supported by one nurse, one health-care assistant, and one clerical staff will be able to manage 800–1600 patients on a recurring basis (depending on their risk profiles) and to implement primary prevention programmes. The

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efficiency of this data-driven and integrated programme can be further enhanced by use of information and communications technology, mobile health, and peer support (appendix p 21).

An example of how quality improvement initiatives driven by research can transform care and inform policies

In Hong Kong, a quality improvement programme driven by research and run by trained non-physician personnel, which was initiated at a university-affiliated hospital to overcome manpower shortage in the early 1990s, has evolved to become a territory-wide programme for risk assessment and management.[459] With simple assessment tools and structured case report forms, a comprehensive set of risk factors and actionable items were collected at referral and every 2–3 years thereafter. On the basis of these clinical data, definition of risk factors and complications can be used to triage care and issue a report card, along with recommended treatment targets and support to promote shared decision making between patients and health-care providers. Similar to the UKPDS Outcome Model,[460] data from the Hong Kong Diabetes Register were linked to hospitalisation records by a unique identifier that allowed the research team to develop algorithms for predicting future risk of complications. In 2007, this structured care protocol with risk stratification was digitalised to become the web-based JADE Technology, which integrates and analyses these data, and issues personalised reports displaying trends of risk factor control and future risk of complications with bars and trend lines. These personalised data were accompanied by recommended treatment targets and decision support triggered by attained targets. By use of integrated care assisted by technology and driven by data, health-care providers can empower self-management, reduce clinical inertia, personalise care, and monitor care quality. Through these regular assessments, care teams can also identify patients with unstable risk factor control and complex phenotypes, such as individuals with young-onset diabetes, atypical presentations, emotional distress, and frailty.[441] Thus, despite the large volume of patients and complex care protocols, it is possible to start improving quality of care and efficiency with teams, logistics, and data analytics. By showing improved care standards and clinical outcomes, these data can motivate decision makers to provide resources for scaling up the operation of these assessment and empowerment services with improved clinical outcomes.[461]

In 2000, hospital administrators created career paths for diabetes nurses to scale up the operation of diabetes centres dedicated to providing assessment (eg, eye, feet, blood, and urine), education, and care coordination. To date, in Hong Kong, with a population of 7·5 million people, there are 18 diabetes centres run by nurses but supervised by endocrinologists in public hospitals, which focus on assessment, education, review, and peer support. Since 2009, primary care clinics based in the community have offered similar risk assessment and management programmes, enhanced by incorporation of the protocol of the JADE Programme.[462] In a 5 year evaluation analysis involving patients with 8 years of disease duration without microvascular or macrovascular complications, the relative risk of any clinical event (including death) was reduced by 50% in participants with diabetes in the risk assessment and management programme (many of whom were also referred to a patient empowerment programme), compared with a propensity score-matched cohort.[463] In a subsequent cost-effectiveness analysis, the absolute risk reduction of participants with diabetes in the risk assessment and management programme ranged from 3 to 13% and the number needed to treat ranged from 7 to 68. With existing infrastructures in the primary care setting and considering the implementation cost of US$157 per individual, including set up and ongoing costs, such as purchase of fundus camera, incorporating risk algorithms into electronic medical records, training nurses to perform the procedures, and patient education, there was an average reduction of $7000 per patient over 5 years after considering all medical costs incurred (eg, consultations, drugs, investigations, and procedures).[463] This cost saving was due to the 2–9 times higher costs of these complications compared with base costs.[464] Taken together, this territory-wide initiative for quality improvement supports the clinical benefits and cost-saving nature of information technology, logistics, and data-driven integrated care, focusing on patient empowerment, feedback, and treatment of multiple targets.

The JADE risk stratification and care model has been adapted by the territory-wide risk assessment and management programme with proven benefits and cost-effectiveness (panel 3).[462,465] By documenting risk profiles at presentation and every 18–24 months thereafter, health-care providers will not only identify care gaps but also measure the independent and combined effects of access to medications, care processes, and diabetes education, as well as self-care, adherence to refilling prescriptions, and attendance of follow-up visits on clinical outcomes. When linked to electronic medical records, hospitalisation data, or other disease registers (eg, end-stage kidney disease, myocardial infarction, cancer, death) that use a unique identifier, these diabetes registers will allow the development of algorithms to predict future risks. These databases also provide important surveillance data and a strong foundation for international research to understand the differences in causes, trajectories, and consequences of diabetes within and between countries. With attainment of treatment targets, access to structured education programmes, and prescription of organ-protective drugs as performance indexes for benchmarking purposes, health-care providers can also promote best practices.

***Panel 3*: Recommended list of data for establishment of a diabetes register for risk stratification, clinical management, and monitoring purposes**

History taking
- Year of assessment*
- Date of birth or age*
- Sex*
- Year of diagnosis of diabetes*
- Duration*
- Type of diabetes*
- Susceptibility to ketosis*
- Highest education attained
- Tobacco use*
- Alcohol use
- Family history of diabetes or maternal hyperglycaemia, renal failure, or premature cardiovascular disease (aged <60 years)
- Vaccination
- Contraception
- History of gestational diabetes

Clinical assessments
- Blood pressure*
- Pulse rate
- Bodyweight*
- Body height*
- Waist circumference*
- Visual acuity*
- Retinopathy (non-proliferative, proliferative, or sight-threatening if available)*
- Foot pulses*
- Skin abnormalities
- Foot deformities
- Sensory neuropathy*

Laboratory tests
- Fasting plasma glucose concentration*
- HbA_{1c}*
- Total cholesterol concentration*
- HDL cholesterol concentration
- LDL cholesterol (or non-HDL cholesterol*) concentration
- Triglyceride concentration*
- Urinary albumin-to-creatinine ratio*
- Plasma creatinine concentration*
- Estimated glomerular filtration rate*
- Blood haemoglobin

Macrovascular complications
- Ischaemic heart disease*
- Heart failure*
- Stroke*
- Non-traumatic lower extremity amputation (below or above knee)*

Microvascular complications
- Foot ulcers*
- Laser or eye surgery*
- Renal transplantation*
- Dialysis*

Comorbidities
- Hyperglycaemic or hypoglycaemic crisis*
- Severe sepsis or chronic infections (eg, tuberculosis, hepatitis B, and hepatitis C)
- Any cancer
- Depression

Oral glucose lowering drugs
- Metformin*
- Sulfonylurea*
- α-glucosidase inhibitors
- Thiazolidinediones
- DPP-4 inhibitors
- SGLT2 inhibitors

Injectables
- Insulin* (brand names, types, regimens, and total daily dose)
- Insulin analogues (brand names, types, regimens, and total daily dose)
- GLP-1 receptor agonists (dose and regimen)

Cardiovascular drugs
- HMG-CoA reductase inhibitors (eg, statins)*
- Renin–angiotensin system inhibitors*
- Aspirin*
- Other drugs that lower blood pressure*
- Other drugs that regulate lipid concentration*
- Other antiplatelet drugs

HbA_{1c}=glycated haemoglobin A_{1c}. *The minimal dataset required in resource-limited settings that should be reported at presentation and every 12–24 months thereafter, as appropriate.

These data on real-world effectiveness[279,466] complement efficacy data from randomised controlled trial settings to guide clinical practice and to identify patient subgroups who are most likely to benefit or to develop adverse events.[441,467]

Use of specialised diabetes centres to promote research and professional education

Professional education is a prerequisite to good clinical care and effective patient education. For example, large-scale audits often showed inappropriate use of insulin (eg, timing, regimen, dosages) by untrained health-care providers, with adverse consequences. In real-world practice, there are considerable delays in the initiation and intensification of insulin, with a lag period of 4–8 years in patients with type 2 diabetes, resulting in persistent exposure to hyperglycaemia.[468] Even if insulin is initiated, absence of titration and self-discontinuation are not uncommon. Inappropriate insulin regimens and excessive use of glucose-lowering drugs can cause severe

hypoglycaemia, which is a leading cause of emergency hospitalisation, especially in older people (aged ≥65 years).[243] Patients with multiple morbidities and polypharmacy will need periodic review of their medications to ensure safety.[469] In the cluster-randomised step-up programme in Australia, an accredited nurse and educator in diabetes served as a mentor and trained nurses working in primary care clinics to initiate and titrate insulin in patients with type 2 diabetes who needed insulin therapy. 105 (70%) of 151 patients managed by trained nurses in these intervention clinics were started on insulin, compared with 25 (22%) of 115 patients in control clinics (ie, managed by nurses who had not received such training).[470] Additionally, patients in these intervention clinics had a 0·6% (6·6 mmol/mol) improvement in HbA_{1c}.

Diabetes management has now become increasingly complex with many technological advancements, including use of multiple medications and injectables, continuous glucose monitoring, insulin delivery systems, and metabolic surgery. There are also emerging technologies, such as the use of biogenetic markers in precision medicine.[471] To ensure that patients receive the full benefits of these advancements, the curriculum of undergraduate programmes needs to expand with ongoing postgraduate and professional training in diabetes and other NCDs. Attending regular conferences organised by professional organisations is essential for updating professional knowledge to improve care. Furthermore, specialised diabetes centres based in hospitals or in the community and often affiliated with academic institutions or major health-care organisations are in a good position to set up accreditation programmes in the management and education of diabetes (eg, certificate, diploma, or master courses). These programmes will help to build a crucial mass of workforce with the right knowledge, skills, and attitudes to provide basic, standard, and comprehensive care in a proactive, effective, and integrated manner as recommended by most professional organisations,[239] including the International Diabetes Federation.[393,472]

These centres, whether based in LMICs or HICs, should have a dedicated space led by one or more physicians with credentials in diabetes management, as well as by nurses with training in diabetes education supported by the appropriate equipment and tools (panel 2). These centres are usually tasked with the management of patients with complex needs (eg, type 1 diabetes; young-onset diabetes; maturity-onset diabetes of the young; type 2 diabetes with comorbidities, including depression), are supported by other health-care professionals (eg, dietitians and podiatrists) and specialists (eg, ophthalmologists, metabolic surgeons, cardiologists, nephrologists, psychiatrists), and work closely with primary care physicians to provide collaborative care. For quality improvement and research purposes, it is recommended that these centres establish registers and ensure that patients are seen at the right time by the right team in the right setting to optimise outcomes.[441] By combining practice, research, and professional training, these centres can take on additional

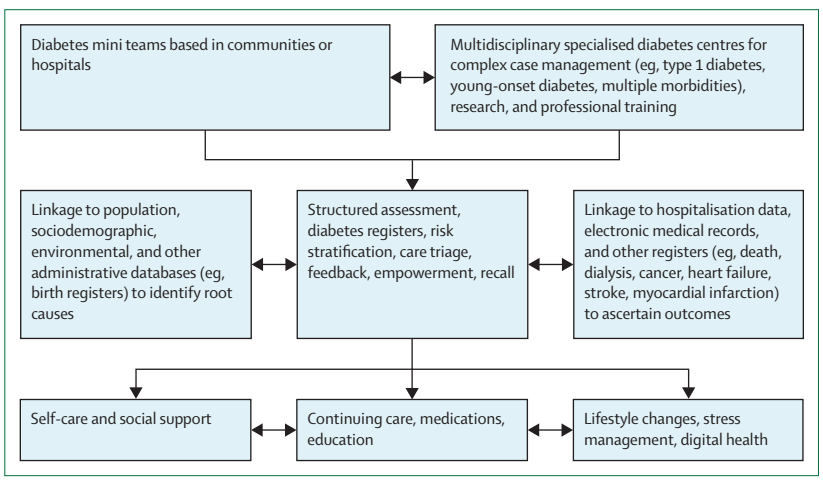

Figure 14: **Combined use of specialised diabetes centres, teams, and registers to integrate professional education, research, and practice with linkage of register data to other databases for clinical audit and surveillance of prevalence (burden) and incidence (intervention) of diabetes and its complications**
The establishment of these prospective cohorts with structured data management accompanied by biobanks will further advance research by discovering causal pathways for precision medicine.

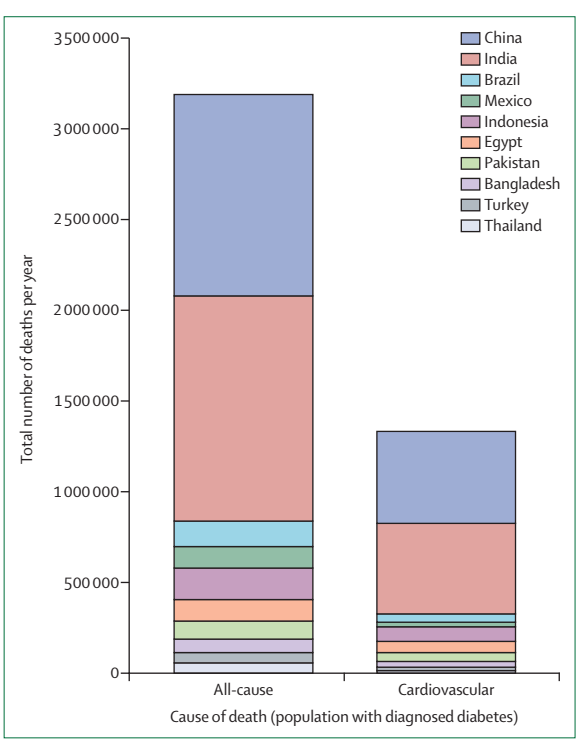

Figure 15: **3 year estimation of all-cause and cardiovascular death in people with diagnosed diabetes (aged 30–69 years) in the top ten low-income and middle-income countries**
Estimation based on data taken from WHO and International Diabetes Federation (2017), and the estimated hazard ratios for all-cause death (1·80 [95% CI 1·71–1·90]) and cardiovascular death (2·32 [2·11–2·56]) from the Emerging Risk Factors Collaboration.[4] For the full references in this figure, see the appendix pp 4–5.

roles of monitoring performance, analysing registers, and developing new programmes to address unmet needs (figure 14). In a prospective cohort of 7488 patients with type 2 diabetes (1986–91) followed up in Italy, patients seen only by family physicians had a higher risk of mortality than did the general population, with an SMR of 1·62 (95% CI 1·51–1·74). This risk fell to 1·44 (1·34–1·54) among patients attending both family physicians and diabetes centres. The 5 year survival probability for patients seen only by family physicians was 0·76 (0·75–0·78) and that of patients attending both family physicians and diabetes centres was 0·81 (0·80–0·82), compared with the general population. Attending diabetes centres was an independent predictor of improved survival, after adjusting for sex, age, and diabetes therapies. Similar benefits were observed for cardiovascular death.[473,474]

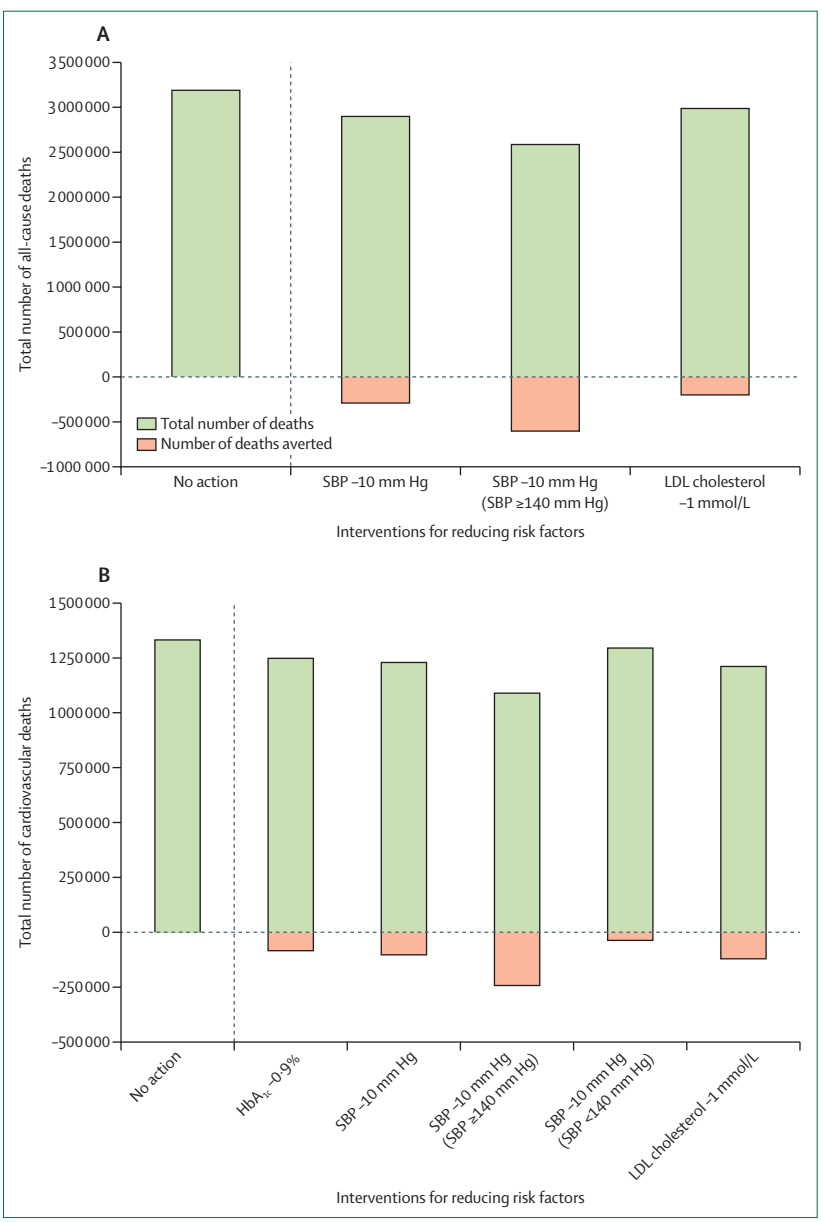

Figure 16: **3 year estimation of all-cause deaths (A) and cardiovascular deaths (B) with status quo and deaths averted with interventions for reducing risk factors in people with diagnosed diabetes (aged 30–69 years) in the top ten low-income and middle-income countries**

These estimates are based on the assumptions that 50% of people with diabetes are diagnosed; 70% of diagnosed patients are treated; there is no change in diabetes prevalence and death rate for 3 years; death rate is equivalent to birth rate; and the effect size is sustained for 3 years. For estimation of effect size of different interventions based on meta-analyses, see appendix pp 4–5. SBP=systolic blood pressure.

Use of simulation models to estimate and compare the effects of no action versus action

In this evidence-based Commission, we put great emphasis on the interdependency of society, population, and community in influencing patient outcomes. In the case of type 1 diabetes, we have quantified the effects of providing comprehensive care in reducing premature death in young individuals. For type 2 diabetes, rapid societal changes have changed our ecosystem, way of living, and access to care, especially in LMICs, which explain a large fraction of the diabetes epidemic, albeit potentially preventable. In turn, the health consequences of this epidemic will have societal consequences, notably health-care expenditure, societal productivity, and quality of life. The complex pathophysiology of diabetes has led to many clinical presentations of diabetes, and people with diabetes and individuals at risk have many needs, beyond medical. Over the past three decades, we have gathered a wealth of data regarding the size of the problem and effects of potential solutions. We have used these data to develop a model to quantify the burden of diabetes and the impact of an integrated prevention and care programme for patients with type 2 diabetes (appendix pp 4–12). This model is available by request to Ping Zhang (US Centers for Disease Control and Prevention, Atlanta, GA, USA) to allow readers to enter local data and to estimate the potential effects of implementing various strategies in their area, organisation, clinical practice, or a combination of all three.

Use of data from the International Diabetes Federation, WHO, and randomised controlled trials to estimate the effects of care access on reducing death and cardiovascular disease in type 2 diabetes

To quantify the impact of this integrated society–population–community strategy (figure 11), we compared the effects of no action versus action by reducing multiple risk factors. We first used WHO's *Global Health Estimates* from 2016 on causes of death[13] and the International Diabetes Federation's *World Diabetes Atlas* from 2017 on diabetes prevalence in individuals aged 30–69 years. We then used the hazard ratios of all-cause deaths (1·8) and deaths related to cardiovascular disease (2·3) associated with diabetes (including diagnosed and undiagnosed) compared with people without diabetes, as reported in the Emerging Risk Factor Collaborative Cohort,[4] to estimate the total

number of deaths attributable to diabetes (appendix pp 4–5). On the basis of these assumptions, we selected the top ten LMICs with the largest population with diabetes, which account for 50% of the global population with diabetes. We modelled this finding among the 109 million individuals (aged 30–69 years) diagnosed with diabetes living in these ten LMICs. Accordingly, an estimated 3·2 million individuals would die after 3 years, of which 1·3 million deaths would be due to cardiovascular disease (figure 15; appendix p 22).

Use of statins, which are available at extremely low costs for generic preparations (even in LMICs), to reduce LDL cholesterol concentration by 1 mmol/L (39 mg/dL) can lower the risk of all-cause death by 9%,[475] and cardiovascular disease and related death by 13%,[212] especially in patients with diabetes who have either high risk of cardiovascular events or LDL cholesterol concentration equal to or higher than 2·6 mmol/L (100 mg/dL). Considering that reducing HbA_{1c} by 1% (11 mmol/mol) might lower risk of cardiovascular events[209] or cardiovascular death by 10%,[210] and

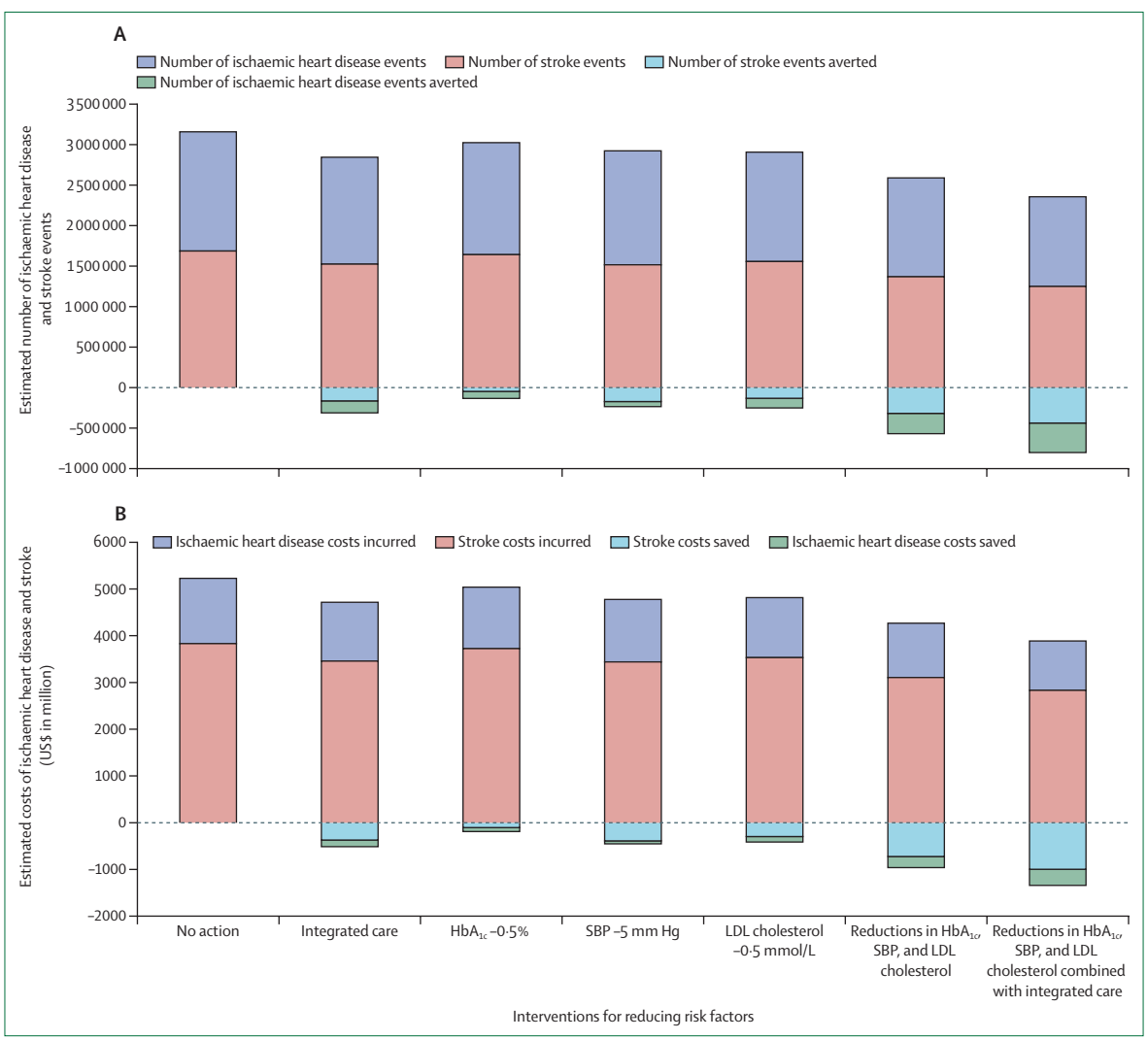

Figure 17: **3 year projection of the incidence and costs of ischaemic heart disease and stroke in people with diagnosed diabetes (aged 20–79 years) in China based on the risk profiles in a surveillance cohort**

Data based on the China non-communicable disease suveillance cohort (HbA_{1c} 7·2%, SBP 144·2 mm Hg, LDL cholesterol 2·59 mmol/L) from Ding and colleagues.[483] These estimates are based on the assumptions that 50% of people with diabetes are diagnosed; 70% of diagnosed patients are treated; diabetes prevalence is maintained for 3 years; and the effect size is sustained for 3 years. (A) Estimated incidence of ischaemic heart disease and stroke events, and events averted with interventions. (B) Estimated costs incurred for ischaemic heart disease and stroke, and costs saved with interventions. In China, the combined public and private direct medical costs per event are US$951 for ischaemic heart disease and $2270 for stroke (no baseline complications assumed). Chronic kidney disease, end-stage kidney disease, and peripheral vascular disease are excluded in the calculation; therefore, these values are underestimations. For estimation of effect size of risk factor reduction and integrated care, as well as direct medical cost (adjusted for age, sex, and cost of living index), see appendix pp 5–8. HbA_{1c}=glycated haemoglobin A_{1c}. SBP=systolic blood pressure.

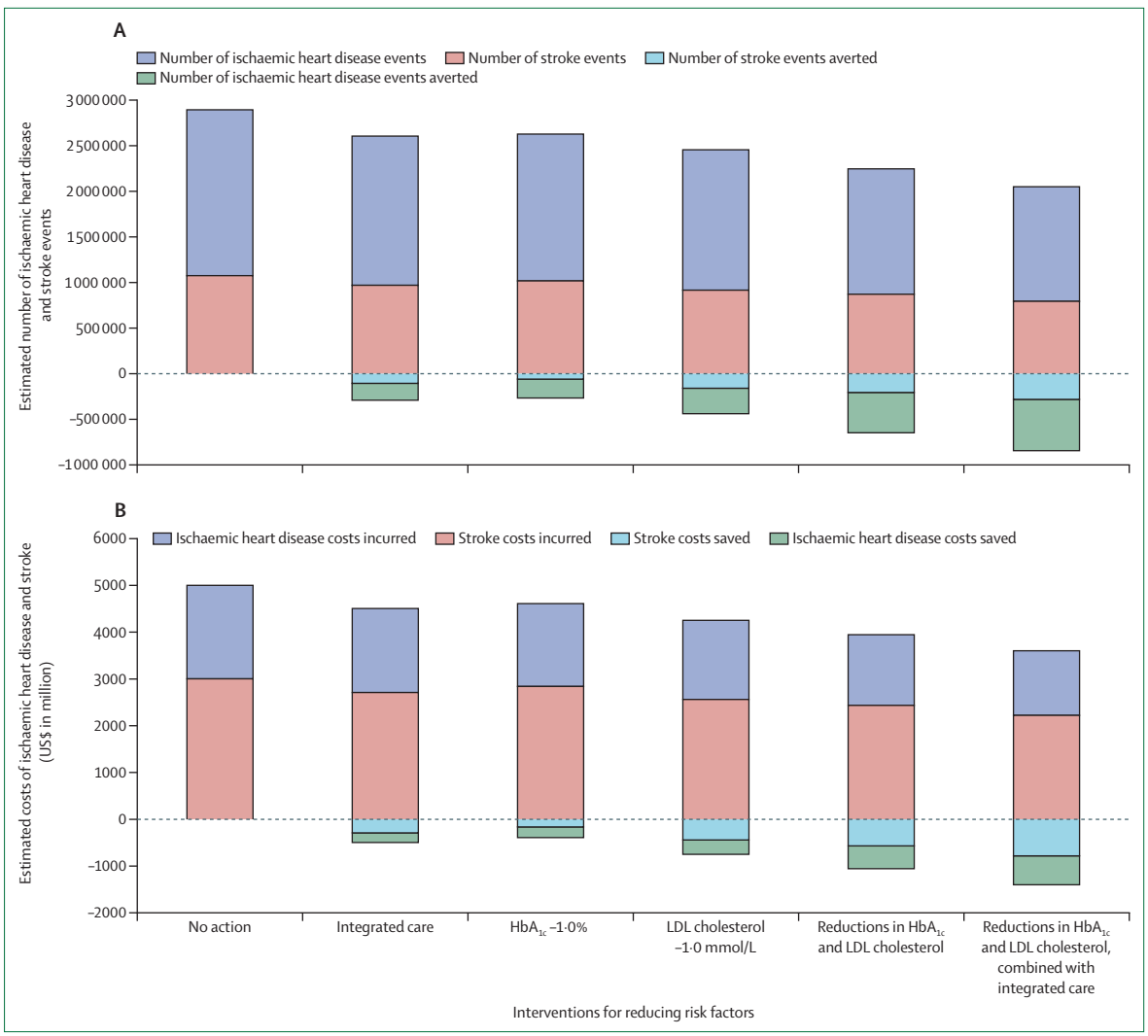

Figure 18: **3 year projection of the incidence and costs of ischaemic heart disease and stroke in people with diagnosed diabetes (aged 20–79 years) in China based on the risk profiles in a clinic-based cohort**

Data based on the China JADE study (HbA_{1c} 7·9%, SBP 125·8 mm Hg, LDL cholesterol 2·94 mmol/L, disease duration 5 years) from Tutino and colleagues.[484] These estimates are based on the assumptions that 50% of people with diabetes are diagnosed; 70% of diagnosed patients are treated; diabetes prevalence is maintained for 3 years; and the effect size is sustained for 3 years. (A) Estimated incidence of ischaemic heart disease and stroke events, and events averted with interventions. (B) Estimated costs incurred for ischaemic heart disease and stroke, and costs saved with interventions. In China, the combined public and private direct medical costs per event are US$1099 for ischaemic heart disease and $2794 for stroke (no baseline complications assumed). Chronic kidney disease, end-stage kidney disease, and peripheral vascular disease are excluded in the calculation; therefore, these values are underestimations. For estimation of effect size of risk factor reduction and integrated care, as well as direct medical cost (adjusted for age, sex, and cost of living index), see appendix pp 5–8. HbA_{1c}=glycated haemoglobin$_{1c}$.

decreasing systolic blood pressure by 10 mm Hg might lower such risks by 20%,[211] we estimate that each of these interventions can reduce cardiovascular disease, all-cause death, or both, by 10–20% (appendix pp 4–5). Although the values of HbA_{1c}, blood pressure, and LDL cholesterol concentration are not known in these populations, we assume that most diagnosed individuals with diabetes can benefit from a further reduction in risk factors. Assuming a diagnosis rate of 50% and by ensuring access to essential medicines in at least 70% of diagnosed individuals (including statins and drugs that lower blood glucose concentration and blood pressure), together with a support system ensuring sustained reduction of these risk factors for 3 years, potentially between 300 000 and 600 000 premature deaths could be averted by reducing blood pressure by 10 mm Hg, depending on baseline measurements. By treating patients with statins to reduce LDL cholesterol concentration by 1 mmol/L (39 mg/dL), another 200 000 all-cause deaths could be averted, thereby averting up to 800 000 premature deaths (figure 16A). By improving each of these three risk factors (ie, HbA_{1c}, LDL cholesterol concentration, and blood pressure), potentially between 30 000 and 240 000 cardiovascular

deaths could be averted, depending on their baseline risk factors (figure 16B).

Use of observational data to develop a risk calculator and use of randomised controlled trial data to estimate effects of interventions

Each person with diabetes is unique with different risk factors, trajectories, complications, and outcomes that can be modified by improving access to care, education, and medications, and by changing behaviours and social habits.[476] In our literature search, few country or territory-wide registers with comprehensive data included non-modifiable risk factors (eg, age, sex, duration of diabetes, complications) and modifiable risk factors (eg, HbA_{1c}, blood pressure, LDL cholesterol concentration, BMI, use of tobacco, self-management, lifestyle), linked to clinical outcomes. Some of these registers came from small countries or areas, such as Sweden and Hong Kong, partly due to their small population size. In these areas, linkage of clinical records to national disease registers, electronic medical records, or hospitalisation records can be facilitated by unique identifiers and use of International Classification of Diseases codes.[61,477] Similar to the UKPDS Outcome Model, including risk equations based on data collected in a randomised controlled trial setting,[460,478] risk equations can be developed by use of real-world databases; however, their external validation might be confounded by ethnicity, locally relevant risk factors, and care standards.[479,480] Nevertheless, with absolute risk prediction, these models can provide useful information regarding the effects of reducing different risk factors with multiple strategies, which can help health-care providers or planners to prioritise their action plans.

Use of HbA_{1c}, blood pressure, and LDL cholesterol to develop an ABC model and to estimate effects of integrated care in 3 years

Although we have curated 40 cross-sectional surveys to provide a global landscape of risk factor distribution in 1·9 million people with type 1 or type 2 diabetes, most of these surveys reported only basic information and did not have details on cardiovascular complications and renal function, both of which are important prognostic factors (figure 7). Therefore, we used commonly reported variables (eg, age, sex, duration of diabetes, use of tobacco, HbA_{1c}, systolic or diastolic blood pressure, LDL cholesterol concentration, and BMI) available in the Hong Kong Diabetes Register and the JADE Register consisting of 22 514 patients with type 2 diabetes (1994–2015) observed for 65 966 patient-years since 1994.[481] Additionally, we used Poisson regression analysis[482] to develop an ABC model to estimate the incidence of cardiovascular disease (including ischaemic heart disease and stroke) and related death for up to 3 years (appendix pp 5–8).

We externally validated this model with the published summary data of two prospective cohorts with reported events. These cohorts included the Hong Kong Diabetes Database, consisting of 212 659 Chinese patients with type 2 diabetes, and the National Swedish Diabetes Register, consisting of 271 174 Swedish patients with type 2 diabetes (appendix p 6). By simulating 1 million patients with a similar profile, the ABC model performed well with the risk ratio of predicted versus observed events approaching 1 (appendix p 6). With this validated model, the 3 year incidence rate of cardiovascular disease in populations with diabetes (aged 20–79 years) with different combinations of risk factors can be estimated. We then estimated the effects of reducing each or all three ABC risk factors (ie, HbA_{1c}, blood pressure, and LDL cholesterol concentration), with the relative risk reduction reported in randomised controlled trials[209–212] (appendix pp 6–8) based on medications alone or combined with provision of integrated care.[276] Provision of integrated care aimed to overcome clinical inertia and non-adherence.[269]

We selected two published cohorts with data needed to run the ABC model. In the China NCD Surveillance Cohort, which predominantly included individuals with newly diagnosed diabetes,[483] mean HbA_{1c} was 7·2% (55 mmol/mol), systolic blood pressure was 144 mm Hg, and LDL cholesterol concentration was 2·59 mmol/L (100 mg/dL). In China, 10% of adults have diabetes.[385]

***Panel 4*: Society, population, and community–based strategies for type 2 diabetes prevention**

Society-based strategy
- Universal secondary school education
- Social inclusion and protection
- Environmental protection

Population-based strategy for promoting health
- Health awareness programme (eg, public education or social media)
- Tobacco control (eg, price, smoke-free area, media, warnings, tax, cessation support)
- Food policies (eg, price, adverts, labelling, tax, media)
  - ensure food security
  - avoid foods with high sugar, salt, and trans-fat content
  - provide subsidy for healthy foods

Community-based strategy for detection and prevention
- Universal health coverage
- Strong primary care system
- Use risk conditions and risk scores to identify individuals at high risk for primary prevention
- Use non-physician personnel to implement diabetes prevention programmes
- Use technology to increase reach, effectiveness, adoption, and maintenance of diabetes prevention programmes
- Early use of metformin, renin–angiotensin system inhibitors, and statins in individuals at high risk to prevent type 2 diabetes, cardiovascular disease, or both

Assuming a 50% diagnosis rate (57 million people) with risk profiles similar to the China NCD Surveillance Cohort,[483] and 40 million (70%) of these diagnosed patients under usual care, we estimated that 3 million of them could develop a cardiovascular event in the next 3 years. By strengthening the system and providing continuing integrated care, which has been shown to reduce HbA_{1c} by 0·51% (5·6 mmol/mol), systolic blood pressure by 2·4 mm Hg, and LDL cholesterol concentration by 0·14 mmol/L (5·4 mg/dL)[276] in at least 70% of these diagnosed individuals, 300 000 cardiovascular events could be averted (figure 17A; appendix p 24).

If control of risk factors was intensified with medications to lower HbA_{1c} by 0·5% (5·5 mmol/mol), LDL cholesterol concentration by 0·5 mmol/L (19 mg/dL), and systolic blood pressure by 5 mm Hg, between 130 000 and 250 000 cardiovascular events could be averted. If all three risk factors were improved, 570 000 cardiovascular events could be averted, which could increase to 800 000 events if these improvements were combined with integrated care (figure 17A; appendix p 24). We used the published costs of diabetic complications in a public health-care setting in Hong Kong,[464] which were adjusted for cost of living index, and we estimated the potential cost saving in these scenarios (appendix p 8). If status quo is maintained, these cardiovascular events will cost the system over US$5200 million, which can be reduced by $1300 million if care is organised and medication use is increased to reduce multiple risk factors (figure 17B; appendix p 24).

In a clinic-based cohort of Chinese patients with type 2 diabetes enrolled in the JADE Register,[484] mean disease duration was 5 years. These patients had better control of blood pressure (125·8 mm Hg), but higher HbA_{1c} (HbA_{1c} 7·9% [63 mmol/mol] and LDL cholesterol concentration 2·94 mmol/L [114 mg/dL]) than did patients in the China NCD Surveillance Cohort.[483] Assuming a 50% diagnosis rate with similar risk profiles, if HbA_{1c} can be reduced by 1% (11 mmol/mol) and LDL cholesterol by 1 mmol/L (39 mg/dL), supported by integrated care in 70% of these diagnosed individuals, 840 000 cardiovascular events and US$1400 million could be saved (figure 18; appendix p 25).

We acknowledge the considerable variations in health-care financing (eg, public, private, partially subsidised) and provider systems (single care providers *vs* multiple care providers) between countries. However, on the basis of data from epidemiological studies and randomised controlled trials, this Commission shows the potential effects of improving access to medications, continuing care, and educating patients at a system level, which could prevent millions of cardiovascular events and save billions of dollars. In this Commission, we emphasise the use of generic medications and non-physician personnel to improve existing care. These benefits have been proven in a technologically assisted, integrated care model in Hong Kong with different risk profiles in public and public–private partnership settings.[459] This cost saving is likely to be underestimated, given the known benefits of reducing risk factors on hospitalisations and other morbidities, quality of life, and societal productivity among affected workforces.

	Country	Number of participants	Intervention	Duration of follow-up	Relative risk reduction (%)
CDQDPS, 1997	China	577	Lifestyle modification	6·0 years	Diet 31·0%; exercise 46·0%; diet plus exercise 42·0%
CDQDPS, 2008	China	577	Lifestyle modification	20·0 years	Diet plus exercise 43·0%
CDQDPS, 2014	China	577	Lifestyle modification	23·0 years	Diet plus exercise 45·0%
DPS, 2001	Finland	522	Lifestyle modification	3·2 years	58·0%
Diabetes Prevention Extended Study, 2013	Finland	522	Lifestyle modification	13·0 years	38·0%
DPP, 2002	USA	3234	Lifestyle modification; metformin	2·8 years	Lifestyle 58·0%; metformin 31·0%
DPPOS, 2009	USA	3234	Lifestyle modification; metformin	10·0 years	Lifestyle 34·0%; metformin 18·0%
DPPOS, 2015	USA	3234	Lifestyle modification; metformin	15·0 years	Lifestyle 27·0%; metformin 18·0%
Prevention of type 2 diabetes by lifestyle intervention, 2005	Japan	458	Lifestyle modification	4·0 years	67·4%
IDDP-1, 2006	India	531	Lifestyle modification; metformin	2·5 years	Lifestyle 28·5%; metformin 26·4%
IDDP-2, 2009	India	407	Lifestyle modification plus pioglitazone	3·0 years	No benefit by adding pioglitazone
Zensharen Study for Prevention of Lifestyle Diseases, 2011	Japan	641	Lifestyle modification	3·0 years	44·0%
Indian SMS Study, 2013	India	537	Lifestyle modification	2·0 years	36·0%
D-CLIP, 2016	India	578	Lifestyle modification plus stepwise addition of metformin (for individuals at highest risk of conversion to diabetes)	3·0 years	32·0%

For the full references in this table, see the appendix p 15.

Table 6: **Major randomised controlled trials in the primary prevention of type 2 diabetes**

Use of a simulation model to estimate the impact of a 20 year society–population–community strategy for preventing type 2 diabetes

We developed a simple Markov microsimulation model[205] to evaluate the short-term, mid-term, and long-term impact of an integrated strategy for preventing type 2 diabetes and cardiovascular disease, compared with status quo or non-intervention. This multicomponent strategy included education–social–environmental policies; population-based health promotion policies; and community-based early detection, prevention, and treatment programmes. This model was developed for meeting the particular needs of this Commission; in other words, it needs to be flexible so that it can be applied

to diverse country settings; be less data-demanding and, instead, make use of data available in most countries, especially low-income countries; and be able to capture the main health impact of preventive programmes (appendix pp 8–11).

By use of published data from China,[485] Hong Kong,[486] and Brazil,[368] we estimated the distribution of risk categories for progression to type 2 diabetes and the number of diabetes and cardiovascular events averted if a hypothetical multicomponent intervention was implemented in 1 million individuals in 5, 10, and 20 years, compared with status quo. The total effect size of this society–population–community strategy (panel 4)[487] is inferred from the relative risks associated with modifiable risk factors reported in observational studies (table 4), and in randomised controlled trials with lifestyle interventions and medications (table 6).

Assuming the best scenario in which governments, regulators, funders, practitioners, industry, and community act together to transform the ecosystem and establish community-based facilities to raise awareness and to identify individuals at high risk for early intervention with linkage to an integrated health-care system, maximal impacts can be made at all levels to reduce type 2 diabetes and cardiovascular events over 20 years. We assume that a societal strategy will reduce the risk of progression from low risk to high risk of diabetes by 5%, and that a combined population-based and community-based approach will reduce the risk of progression to type 2 diabetes and cardiovascular disease by 25%. On the basis of data from population-based surveys, we estimate the proportion of distribution of cardiometabolic risk factors (BMI, blood pressure, smoking, lipids, HbA_{1c}) in different age groups and the annual probability of transition from low risk to high risk for diabetes and from high risk for diabetes to diabetes. The annual incidence of cardiovascular disease is estimated from the risk equation in the 2013 American College of Cardiology–American Heart Association Guideline on the Assessment of Cardiovascular Risk with common risk factors, including age, sex, smoking, lipids, HbA_{1c}, and BMI.[488]

This model estimates the total and cumulative effects of these health policies and system changes over 20 years. The effects of population-based strategies, such as tobacco control and taxes for sugar-sweetened beverages, applies to the entire populations for reduction of risk factors (panel 4). The effects of community-based strategies, such as intensive lifestyle intervention or metformin use, applies to the population at high risk of type 2 diabetes. Early use of organ-protective drugs, such as statins and renin–angiotensin system inhibitors, applies to the population at high risk of cardiovascular disease (eg, hypertension, obesity, dyslipidaemia). The strengthening of health-care systems through capacity building enables early detection and intervention of these individuals at high risk. In support of this multicomponent strategy, there is now evidence suggesting that prevention of type 2 diabetes will translate into long-term reduction of cardiovascular disease.[258] Although the use of statins and renin–angiotensin system inhibitors can prevent the risk of cardiovascular disease by 20–40% in individuals at high risk, with or without type 2 diabetes,[376] the implementation

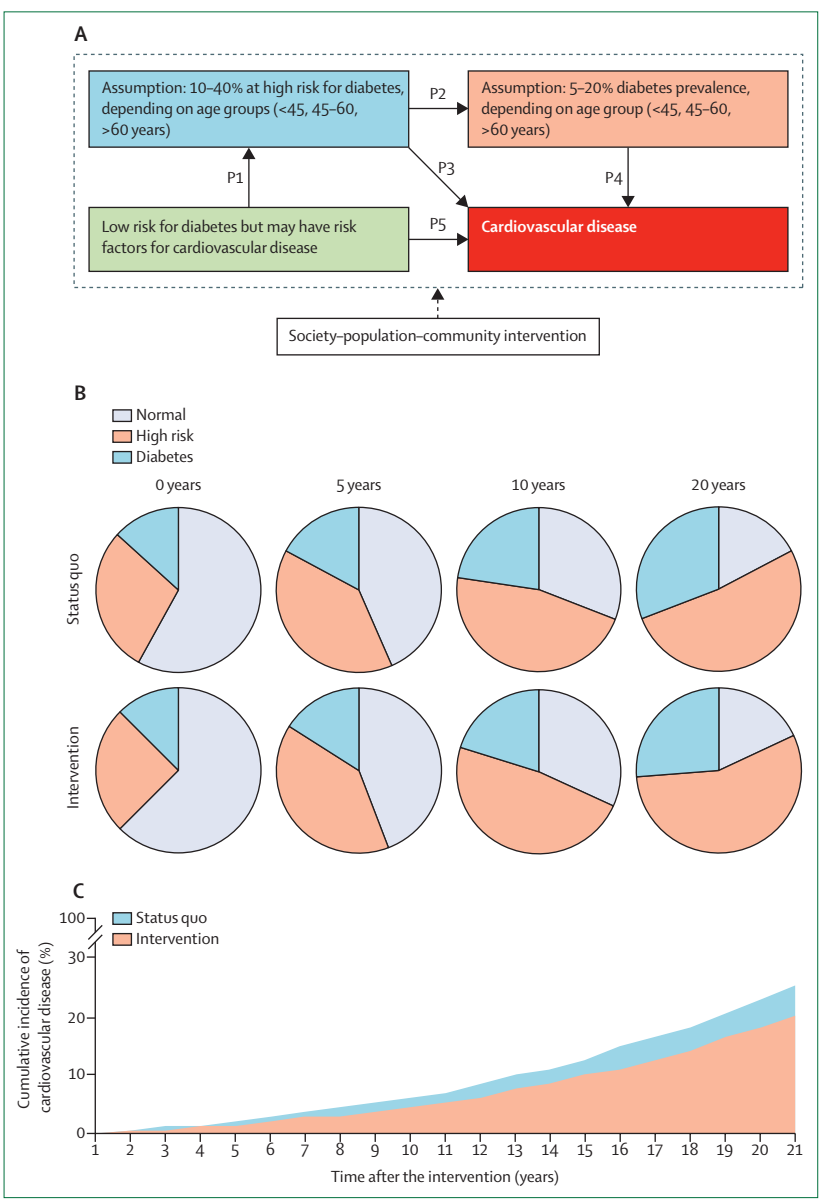

Figure 19: **Effects of an integrated society–population–community intervention on the number of diabetes and cardiovascular events in 1 million people in China over 20 years**

(A) 20 year projection and cumulative incidence of diabetes (B) and cardiovascular disease (C) in 1 million people in China with an integrated society–population–community intervention aiming to improve health environment, reduce population risk, and implement structured lifestyle modifications for individuals at high risk. P1 refers to the annual probability of transition to high risk for diabetes (5–10%); P2 refers to the annual probability of transition from high risk to incident diabetes (1·9–3·8%); and P3, P4, and P5 refer to the annual probability of transition to cardiovascular disease based on the 2013 American College of Cardiology and American Heart Association atherosclerotic cardiovascular disease risk equation to cardiovascular disease. For distribution of cardiometabolic risk factors and annual probabilities of transition to diabetes and cardiovascular disease in different risk categories, see appendix pp 8–11.

of integrated diabetes care can reduce cardiovascular events by 50%.[459]

Assuming that we can successfully implement all components within this strategy in an integrated manner, for every 1 million adults over the next 10 years, 22 489 diabetes events and 17 270 cardiovascular events could be averted. After 20 years, 33 733 diabetes events and 51 863 cardiovascular events could be averted (figure 19; appendix pp 10–11). These figures translate to prevention of type 2 diabetes in 44 million adults and that of cardiovascular events in 67 million adults for a population of 1·3 billion in China alone. Similar effects could be seen in a population of 130 million in Brazil in 2017 (figure 20; appendix pp 10–11).

Use of unified data management to track disease burden, measure effects, and inform policies

The total prevalence of diabetes reflects disease burden; age-sex-specific prevalence rates allow for comparisons between populations; the ratio of diagnosed to undiagnosed diabetes reflects effectiveness of case finding and follow-up programmes; and age-sex-specific incidence rates of type 2 diabetes reflect the effects of interventions, among other factors. These factors include, but are not limited to, political, socioeconomical, and technological changes within a population, area, or both. Given the silent and progressive nature of diabetes and its complications, we discussed the utility of a prospectively designed and unified data management system to support the collective needs of clinical, surveillance, and research activities to create impact.[489]

It is crucially important to distinguish the meaning of prevalence, as a measure of disease burden, from incidence, as a measure of risk. Thus, the relentless increase in the prevalence of diabetes can be disheartening, despite the efforts from many governments, organisations, and individuals to fight the epidemic. However, as long as the death rate is lower than the incidence rate, the prevalence of diabetes will continue to increase. Ageing and increased awareness with early diagnosis, which inflate prevalence, are other factors that should be considered before prevention programmes are judged as being ineffective. Although surveys have been done on millions of individuals worldwide, the data derived from these surveys have serious limitations. For example, of 200 countries analysed by the NCD Risk Factor Collaboration,[6] 146 countries had population-based data that included direct measures of glycaemia, but only 108 countries had national data. The countries with fewest data were located in central Africa, the Caribbean, and central Asia. Even when studies were available, younger (aged <40 years) or older (aged >70 years) adults were sometimes not enrolled. Other data limitations include increasingly low response rates (especially in HICs) and different definitions of diabetes (eg, fasting plasma glucose concentration, 75 g oral glucose tolerance test, HbA_{1c}). As a result, it is difficult to compare prevalence between populations and track it over time, even within the same country. For studies with more than one of these measures, the difficulty is compounded by variations in how the measures are combined to define diabetes.

The most common source of incidence data was the classical longitudinal cohort study. Unfortunately, such cohort studies are unable to provide reliable estimates of how incidence changes over time. There are several reasons for this. First, high cost aside, it has proven difficult to obtain sufficiently high response and follow-up rates to be certain that they are representative of a national or regional population. Second, cohort sizes of several tens of thousands of people would be required to adequately power comparisons of changes in incidence over relevant time periods. Third, and perhaps most importantly, comparisons over time require either a series of independent cohorts or a so-called open cohort design, in which new participants regularly enter the cohort. In practice, this approach rarely occurs, meaning that alternative sources are needed to establish secular trends.

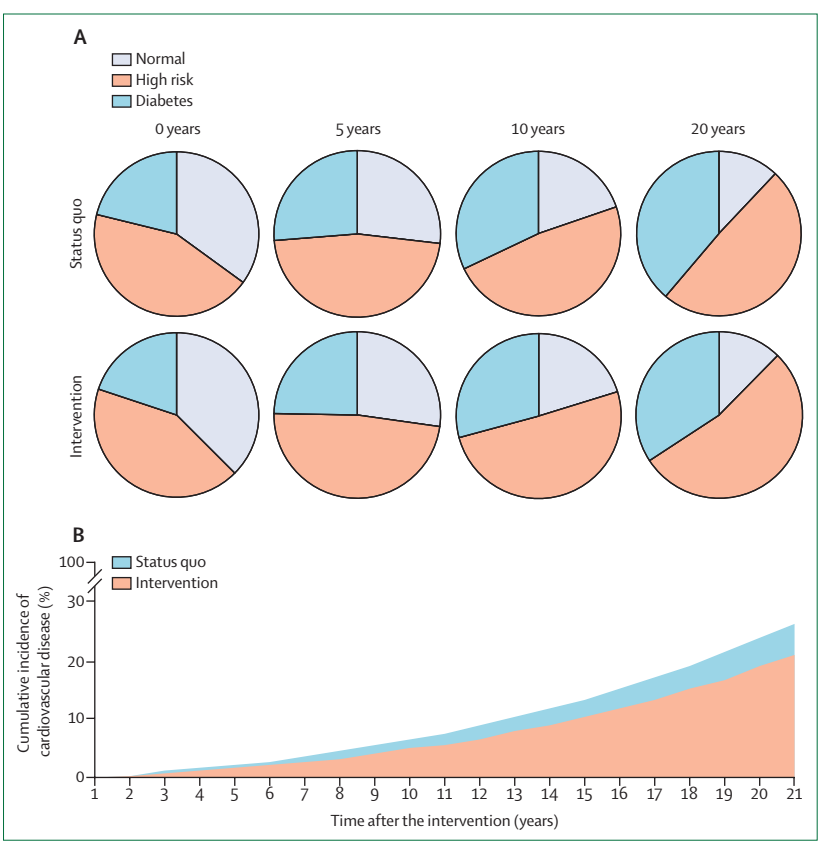

Figure 20: **Effects of an integrated society–population–community intervention on the number of diabetes and cardiovascular events in 1 million people in Brazil over 20 years**

20 year projection and cumulative incidence of diabetes (A) and cardiovascular disease (B) in 1 million people in Brazil with or without an integrated society–population–community strategy aiming to improve health environment, reduce population risk, and implement structured lifestyle modifications for individuals at high risk. For distribution of cardiometabolic risk factors and annual probabilities of transition to diabetes and cardiovascular disease in different risk categories, see appendix pp 8–11.

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Utility of administrative databases and registers to monitor prevalence and incidence

Given the inability of standard longitudinal cohort studies to report incidence trends meaningfully, administrative data can make a crucial contribution to inform clinical and public health practice. We have discussed use of electronic medical records within the context of analysing data to identify gaps and to improve care. Additionally, we presented some of the opportunities of data analytics for surveillance purposes. With increasing use of digital information, administrative databases are often populated with data from various sources, including dedicated disease registers, insurance claims, and electronic medical records. The strengths of these databases include their large size (typically >100 000 individual cases), absence of susceptibility to volunteer bias or loss to follow-up, capacity to produce year-on-year data at a relatively low cost, and ability to explore effects in different subgroups. Their limitations relate mainly to the origin of the data being collected in ordinary clinical practice, often with data omission, rather than in research settings.

Unless data are collected in a structured manner, there is uncertainty about how, and how well, diabetes has been diagnosed and classified into types (eg, type 1 or type 2 diabetes, diabetes in pregnancy, etc). Because most adults with newly diagnosed diabetes have type 2 diabetes, the total incidence is a good proxy for the incidence of this type of diabetes. However, changes in diagnostic criteria can have uncertain effects on observed incidence, depending on the rate at which the uptake of such changes has occurred. Also, there is no measure of undiagnosed diabetes and changes in screening behaviour can confound analysis of secular trends in the incidence of clinically diagnosed diabetes. Analysis of secular trends in data sources that rely on the use of glucose-lowering drugs to identify diabetes status can be confounded by changes in prescribing behaviour.

Despite these limitations, the feasibility of population-based electronic medical records in measuring prevalence, incidence, and secular trends has been shown in some countries or areas with a national or territory-wide database, with most of these places having universal health coverage. The design of these electronic medical records can serve as a reference for other clinical populations, in which similar data are not available due to resources or system factors. For clinical management and quality assurance purposes, various clinical and laboratory measurements are required for collection at diagnosis and regular intervals (eg, every 2–3 years; panel 3). By redesigning workflow and applying a team approach to set up registers, these data gaps can be filled. By use of a unique identifier, these databases can be linked to population statistics collected during census or by other governmental departments, such as sociodemographic[490] and meteorological data.[132]

For accounting purposes, digitalisation of hospitalisation records and disease registers are increasing (eg, cancer, ischaemic heart disease, coronary interventions, heart failure, dialysis, depression).[491] In some countries where establishment of a national diabetes register is not practical, supporting a consortium of diabetes teams to collect data in a structured manner during their routine clinical practice might be an alternative. By combining structured databases with population statistics, electronic medical records, and disease registers, health-care providers can identify upstream determinants, uncover treatment gaps, classify patient subgroups, perform analytics, and evaluate the effectiveness of medications in real-world practice.[492] In some areas where large-scale data from randomised controlled trials are not available, these databases can be used to verify their effectiveness in real-world practice. For example, in Asia, these databases have been used to substantiate the benefits of statins in reducing cardiovascular events,[493] including peripheral arterial disease[494] and chronic kidney disease,[495] and to inform practice, albeit randomised controlled trials are the gold standard. By sharing these best practices and real-world data, comparative analysis on diabetes epidemiology and care standards in different populations and settings can be done to advocate for improved management and prevention of diabetes.[441,496]

Electronic medical records and administrative databases suggest decreasing diabetes incidence in some countries

Many of these electronic medical records and registers were established through introduction of quality improvement programmes whereby care organisation has resulted in structured collection of real-world data, which has enabled the systematic analysis of clinical outcomes and effectiveness of interventions.[497] The availability of these data has also motivated decision makers to invest in these programmes and to increase their impact.[496] In Israel, analysis of a large insurance group showed an 18% decrease in diabetes incidence during 2006–12.[498] Analysis of claims data in the USA showed a decrease in incidence from 1·0% to 0·65% during 2007–12.[499] Data from the Korean Health Insurance Database showed a decrease in incidence during 2005–09 and a consequent period of stabilisation until 2012.[500] In Hong Kong, although stabilising incidence trends in middle-aged people (aged 40–59 years) and decreasing trends in older people (aged ≥60 years) were observed between 2001 and 2016, diabetes incidence increased substantially in individuals aged younger than 40 years (from 75·4 to 110·8 per 100 000 person-years in men and from 45·0 to 62·1 per 100 000 person-years in women).[52] Stabilisation of incidence has also been reported from a consortium of 11 integrated health-care delivery systems with electronic medical records in ten states across the USA during

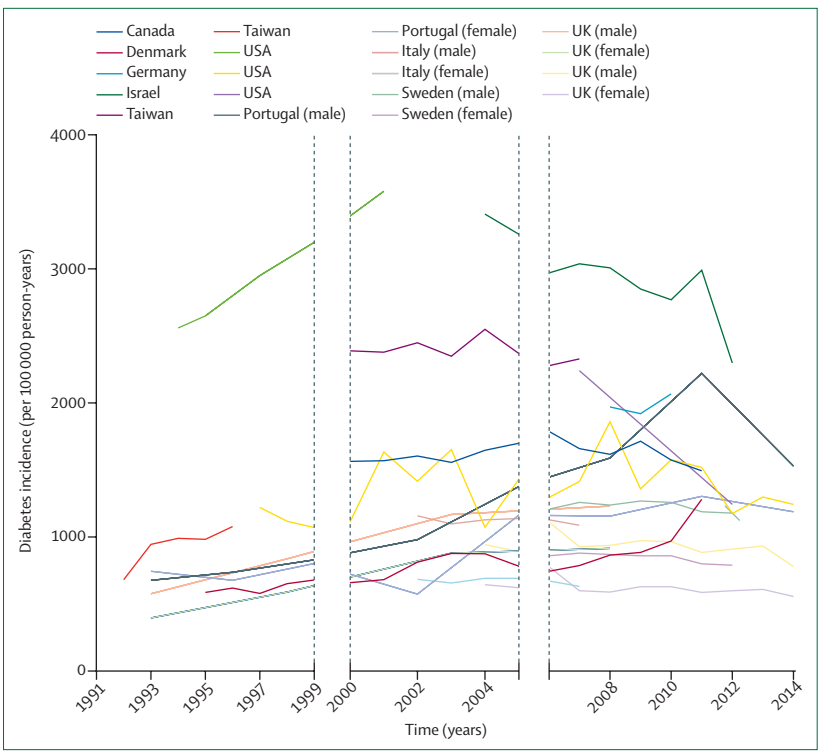

Figure 21: **Global trends in the annual incidence of diabetes among people aged 55–69 years, 1992–2014**
Most decreasing trends occur in high-income countries, with paucity of information in low-income and middle-income countries. These data highlight the importance of societal determinants in which key upstream factors; notably, improved education system, good governance, and social policies in high-income countries, might underline these favorable trends. These results support the call for strategies at a population and individual level for the prevention and control of diabetes and non-communicable diseases. Reproduced from Magliano et al,[2] by permission of *British Medical Journal*. For the full references in this figure, see the appendix pp 26–27.

2006–11,[501] and that of the Scottish National Register in 2004–13.[502] By contrast, studies from England and Wales (1994–98),[503] Portugal (1992–2015),[504] and Canada (1995–2007)[505] reported increases in diabetes incidence.

The first attempt to systematically collate published data on the trends of diabetes incidence in adults (mainly due to type 2 diabetes) showed that most studies came from administrative data sources, rather than health surveys. Although most studies reported increasing incidence between 1990 and 2005, from 2006 to 2014, 27% of reported populations had stable incidence over time, and 36% of populations reported a decreasing trend. Only 36% of populations reported an increasing trend in the incidence of diabetes (figure 21). The studies predominantly came from HICs, and trends might be different in LMICs. Furthermore, most studies could not establish the difference between a true reduction in incidence and a change in diagnostic and screening behaviour.[2] Nevertheless, these encouraging trends contrast with the rising prevalence as reported as the main index in most analyses. With increasing popularity and adoption of electronic medical records and data digitalisation in high-income and middle-income countries, many of which are undergoing major health-care reforms, use of administrative databases to record incidence and prevalence has become increasingly feasible.

Use of data analytics to practise precision medicine and to discover new knowledge

By creating these registers, electronic medical records, population statistics, health surveys, and cohort analysis, researchers can start to identify the linkage between causes, interventions, and outcomes. On the basis of such, algorithms and models can be developed for cross validation, as shown in our case study of China. These context-relevant models or algorithms can be used to prioritise interventions and to identify patient subgroups that can be matched to different strategies to maximise benefits and minimise harm with cost-effectiveness analysis. By establishing biobanks to accompany these databases and cohorts, researchers, practitioners, and analysts can collaborate to discover the inter-relationships between genotypes, phenotypes, treatment, and clinical outcomes in pursuit of precision medicine. At the same time, these rich data sources will provide an important resource for discovery of novel disease pathways and companion diagnostics for predicting, preventing, and personalising diabetes care with participation of individuals with or at risk of having diabetes through education, engagement, and empowerment.[471]

Conclusion

In this *Lancet* Commission on diabetes, we have summarised the global burden of diabetes and emphasised the achievements made in diagnosis and treatment through large-scale epidemiological surveys and randomised controlled trials. We have highlighted the utility of structured data collection through quality improvement programmes to improve care standards and monitor clinical outcomes. Where such structured data were available, we were able to show the decreasing trends of incidence of diabetes and its complications. By use of these databases, we also observed emerging trends and unmet needs in subpopulations. Apart from multiple morbidities, including frailty, depression, and cognitive decline associated with ageing and long disease duration, the high rates of cardiovasular–renal events and death in patients with young-onset diabetes associated with multiple causes and phenotypes re-emphasise the importance of structured risk assessment and management to detect and intervene early.

Although improvements have been reported in some populations, social and care disparity are major health-care barriers in many subpopulations, notably migrant, minor ethnicity, and underserved populations in many HICs. Given the life-course of diabetes, early prevention of obesity by promoting maternal and child health holds promise in curbing the epidemic of diabetes and other NCDs that can go beyond our current generation. To

implement what we have learned and created to benefit individuals with or at risk of having diabetes, and to make our health care sustainable, there is an urgent need to reorganise care by training non-physician personnel and applying a team approach, assisted by information and communications technology, to deliver data-driven integrated care to empower self-management and reduce multiple risk factors. To achieve this system change, alignment among payers, planners, and providers are needed to address the pluralistic needs of patients. Meanwhile, additional research is needed to understand patient-important outcomes, including values, preferences, and psychosocial and cultural factors, which influence lifestyle, self-management, and health-seeking behaviours.

Although globalisation has raised living standards in many people living in LMICs, it has also substantially changed the ecosystem and human behaviours, especially in many emerging economies. In areas hit hardest by the diabetes epidemic, the ill prepared health-care system, minimal capacity, and insufficient data to guide actions have led to most people with diabetes not having their condition diagnosed, treated, or controlled. However, examples from both HICs and LMICs have shown that by implementing a society–population–community strategy, we can potentially reduce the impact of diabetes and other NCDs by creating a health-enabling environment and by strengthening health-care systems.

The global challenge of diabetes transcends political, economic, social, and technological domains. By protecting our environment, changing our practice, and empowering our communities, we can reduce the burden of diabetes as a root cause of many NCDs. The diabetes epidemic is a high calling that concerns all of us, as global citizens who have contributed to the ecosystem in one way or another to fuel the epidemic. As such, we all have the collective responsibility to rise to this great challenge to sustain our environment and to use our finite resources wisely to preserve humanity.

Contributors

JCNC (chair) and EWG (co-chair) invited other members of the Commission (AOYL, JES, BO, NJW, JJG, GDO, TJO, PMC, PZ, CAA-S, PHB, MJD, BE, ME, RRH, APSK, NSL, RCWM, MM, GN, AR, MIS, YS, and W-YS), raised funds, convened face to face meetings, provided the initial direction, and coordinated all communications and subsequent writing. AOYL and JES co-led and prepared the first draft on the section on epidemiology; BO and NJW co-led and prepared the first draft on the section on prevention; JCNC and JJG co-led and prepared the first draft on the section on care delivery; GDO and TJO co-led and prepared the first draft on the section on type 1 diabetes; MIS and RCWM co-led and prepared the first draft on the section on intergenerational diabetes; and PMC and PZ co-led and prepared the first draft on economics. Other researchers and experts with relevant experience (L-LL, ESHL, JA, PB, NGF, GAG, JG, XH, ELK, DJM, B-PN, DO, JP, MP, HS, NU, MW, CW) were invited by various co-leads to review literature, curate data and synthesise evidence relevant to the section. ESHL, L-LL, HS, GAG, ELK, JG, and PB contributed to model development under the guidance of PMC, PZ, GDO, and TJO with further input from RRH, ME, EWG, and JCNC. All members of the Commission contributed fully to the overall report structure and concepts, the writing and editing of the executive summary, and key messages and recommendations. JCNC and EWG collated all sections, wrote the introduction and conclusion, prepared the first draft of the Commission report with further editing from all Commissioners. All members of the Commissioners contributed to the responses to reviewers and editing of subsequent drafts and final report. JCNC and EWG approved the final version of the report.

Declaration of interests

JCNC reports grants from AstraZeneca, Lilly, Lee Powder, Hua Medicine, and Qualigenics; and grants and personal fees from Bayer, Boehringer Ingelheim, Sanofi, Novartis, Merck, and MSD, outside of the submitted work. JCNC also reports being the Chief Executive Officer (pro-bono) of the Asia Diabetes Foundation and a co-founder of GemVCare, during the conduct of this Commission. JCNC also has a patent for genetic markers for diabetes and its complications issued. L-LL reports grants, personal fees, and non-financial support from AstraZeneca, Boehringer Ingelheim, Merck Serono, MSD, Novo Nordisk, Pfizer, Procter and Gamble Health, Sanofi, and Servier; and personal fees from Novartis, outside of the submitted work. JES reports personal fees from AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, Mylan Pharmaceuticals, Boehringer Ingelheim, MSD, and Abbott, outside of the submitted work. TJO reports personal fees from Boehringer Mannheim, outside of the submitted work. BE reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Mundipharma, Navamedic, NovoNordisk, and RLS Global; and grants and personal fees from Sanofi, outside of the submitted work. APSK reports honorarium for consultancy or giving lectures from Abbott, AstraZeneca, Bayer, and Eli-Lilly. ME reports grants from AstraZeneca and Young Health Programme; and personal fees from Prudential, outside of the submitted work. JA reports grants from Medical Research Council (grant code MR/K023187/1), during the conduct of this Commission. NGF reports grants from Medical Research Council Epidemiology Unit, during the conduct of this Commission. DO reports support by Medical Research Council. RCWM reports grants from AstraZeneca, Bayer, Pfizer, Novo Nordisk, Sanofi, and Tricida; speaker's fees from Boehringer Ingelheim donated to the Chinese University of Hong Kong; personal fees from Worldwide Initiative for Diabetes Education (WorldWIDE Diabetes), outside of the submitted work. RCWM also co-founded a technology start-up that provides genetic testing for diabetes and diabetes complications through support from the Hong Kong Government Innovation and Technology Commission and its Technology Start-up Support Scheme for Universities, with no income or remuneration received from the company. YS has received consulting or lecture fees from MSD, Kao, Taisho, Boehringer Ingelheim, Becton Dickinson, Takeda, and Novo Nordisk; and research support from Boehringer Ingelheim, Ono, Arkray Marketing, Sumitomo Dainippon, Taisho, Takeda, and Novo Nordisk. AOYL reports non-financial support from AstraZeneca and Boehringer Ingelheim; grants and non-financial support from Sanofi Hong Kong; non-financial support from MSD; grants from Amgen; and serving as principal investigator for clinical trials sponsored by Bayer, Roche, Lee's Pharmaceutical, and MSD, outside of the submitted work. MJD has acted as consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, MSD, Boehringer Ingelheim, AstraZeneca, and Janssen; an advisory board member for Servier and Gilead Sciences; and a speaker for Napp, Mitsubishi Tanabe Pharma Corporation, and Takeda Pharmaceuticals International. MJD has also received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca, and Janssen. RRH reports grants from AstraZeneca; grants and personal fees from Bayer AG and MSD; and personal fees from Novartis and Novo Nordisk, outside of the submitted work. All other authors declare no competing interests.

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