# Use Data To Transform Diabetes Care And Lives With Diabetes
# The Lancet Commission on Diabetes

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## Executive Summary

2020 will go down in history as the year when the global community is awakened to the fragility of human health and the inter-dependence of ecosystem, economy and humanity. In the midst of the pandemic of coronavirus disease (COVID)-19, the vulnerability of people with diabetes during emergencies became fully evident by their 3–5 fold increased risk of severe disease including death, especially in those with poorly controlled diabetes and/or comorbidities versus those without diabetes, with consequential heavy tolls on healthcare systems and the global economy.

In this Lancet Commission on Diabetes which embodies four years of extensive work on data curation, synthesis and modelling, we urge policymakers, payers and planners to collectively change the ecosystem, build capacity and improve practice environment to enable practitioners to systematically collect data during routine practice and use the data more 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 (NCDs). The emerging evidence regarding the possible damaging effects of coronavirus on beta-cells implies possible worsening of these two pandemics of diabetes and COVID-19 infection, adding to the urgency of these collective actions.

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

Globally, in 2019, 463 million people had diabetes with 80% coming from low- and middle-income countries (LMICs). Over 70% of global deaths are due to NCDs including diabetes, cardiovascular disease (CVD), cancer and respiratory disease. On average, diabetes reduces life expectancy in middle-aged people by a mean of 4–10 years and independently increases the risk of CVD, renal and cancer deaths by 1.3–3.0 fold. It is amongst 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 epidemic, we explain how the concept of environment-agent-host interactions, often used to explain marked variations in risk exposure and outcomes in communicable disease, also applied to diabetes where ecosystem and human behaviours are key upstream factors. In this light, we highlight the impacts of maternal hyperglycaemia on adolescent obesity and the emerging epidemic of young-onset diabetes (YOD) with multiple aetiologies, and their high risk of premature death and complications. Apart from ageing, environmental and socioeconomic factors, notable underlying risk associations of diabetes especially in underserved communities are poor nutrition, physical inactivity, depression, poverty and low levels of education. The multidimensional nature of these risk factors calls for a wide-ranging society-community-individual strategy to integrate prevention, diagnosis and care of type 2 diabetes (T2D).

Despite the availability of efficacious medications proven to reduce cardiovascular-renal events and death rates in clinical trial settings, their lack of provision and access to trained healthcare providers (HCPs) 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 more systematic approach to stratify risk, classify disease subtypes, identify specific needs and personalise care. With regards to type 1 diabetes (TID), we present the continuing high standardised mortality ratios (SMRs), especially in those living in deprived communities and LMICs. Poor access to life-saving technologies, including insulin and blood glucose monitoring tools, as well as inadequate education for self-management have resulted in many avoidable deaths and acute emergencies in these young patients.

Based on best evidence and best practices, we summarise the benefits of more effective management of multiple risk factors among patients with diagnosed diabetes where 1) sustained weight reduction in obese patients by 15 kg or more can induce remission in T2D for up to 2 years; 2) reducing glycated haemoglobin ($HbA_{1c}$) by 0.9% (10 mmol/mol), systolic blood pressure (BP) by 10 mmHg and/or low-density lipoprotein cholesterol (LDL-cholesterol) by 1 mmol/L (39 mg/dL) can each independently reduce the risk of CVD and/or all-cause death by 10–20% in T2D; 3) reducing multiple risk factors including the use of statins and renin-angiotensin system inhibitors (RASi) can prevent cardiovascular-renal events by 20–40% in individuals with or at risk of having diabetes; 4) using sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1-RA) can reduce cardiovascular-renal events and death rates by up to 40% independent of their blood glucose lowering effect; 5) using data-driven, team-based integrated care by re-organising health care provision can reduce CVD and all-cause death in T2D by 20–60%; and 6) implementing structured lifestyle intervention and metformin use can each prevent or delay T2D in individuals with impaired glucose tolerance by 30–50%.

In order to translate these evidence-based risk reduction strategies, we put together an implementation plan showing how by training non-physician personnel to form a diabetes team, we can re-design workflow and use information and communication technology (ICT) to set up diabetes registers and use the data collected to empower self-management, improve provider-patient communication and reduce multiple risk factors. Using this multicomponent strategy, we can identify high-risk patients with T1D, YOD, and those with comorbidities, atypical diabetes and complex needs who require inter-disciplinary management with ongoing support. By using prospectively designed and unified data-management systems, we can support the collective needs of clinical, surveillance and research activities related to diabetes and create societal impacts by transforming care and informing policies.

Using modelling, we have estimated the impacts of our proposed 'integrated actions' versus the current 'fragmented actions'. In high-income countries (HICs), the SMR for patients with T1D is 2.5 compared to that of 4.9–33.9 in LMICs. In 2017, 1.1 million young patients had T1D diagnosed under the age of 20 years and an estimated 14,466 aged less than 25 years died. If all patients with T1D were to receive guideline-based comprehensive care with access to intensive insulin therapy, personalised education and regular complications assessments, we estimate that 12,092 of these deaths could have been averted. For T2D, in 2017, 217 million affected individuals (age 30–69 years) lived in 10 LMICs and 3.2 million are estimated to have died after 3 years with 1.3 million of these deaths due to CVD. By ensuring access to essential medications and improving control of BP, $HbA_{1c}$ and LDL-cholesterol in 70% of diagnosed patients, we estimate 0.8 million of these premature deaths might have been prevented.

If a society-community-individual strategy aimed at reducing illiteracy and social disparity as well as creating a health-enabling environment supported by a community-based health-promoting policy linked to an integrated care system were to be implemented, for a population of 1 million in China, we could potentially avert the occurrence of 11,065 cases of diabetes and 6617 CVD events in the next 5 years, which would increase to 33,773 and 51,863, respectively, after 20 years. These figures would translate to 44 million fewer cases of diabetes and 67 million fewer CVD events in the 1.3 billion Chinese population.

**Key messages**

1. The ensured access to insulin, patient education and blood glucose monitoring tools can prevent premature deaths and emergencies in young patients with T1D especially in disadvantaged communities.
2. The impact of maternal hyperglycaemia on childhood obesity requires a multicomponent lifecourse strategy to prevent YOD which may benefit our next generation.
3. The complex aetiologies, notably psychosocial needs especially in YOD, call for structured assessment in order to personalise care for reducing premature NCD and death.

4. The diverse environmental, behavioural, and socioeconomic causes of T2D require a multitiered societal and population-based prevention strategy.
5. The marked differences in diabetes diagnosis, treatment and outcomes between LMICs and HICs are likely due to differences in investment, capacity, healthcare systems and care organisation.
6. The sustained reduction of common cardiometabolic risk factors including smoking cessation, and use of statins, RASi, SGLT2i and GLP1-RA therapies can reduce cardiovascular-renal diseases and all-cause death in patients with T2D.
7. The delivery of team-based care can enable systematic collection of data during routine clinical practice to improve the quality of electronic medical records (EMR) and establish registers for surveillance, prevention and treatment.
8. The strengthening of existing infrastructures for providing long-term care and creating career paths for physicians with knowledge and skills to re-organise diabetes care, train non-physician personnel and use technology effectively can improve the accessibility, sustainability and affordability of diabetes prevention and care.

**Recommendations**

We recommend the establishment of a Global Diabetes and NCD Task Force, led by policymakers, consisting of stakeholders across different sectors, including but are not limited to, healthcare institutions, academia, school, industry, professional bodies/experts, nongovernment organisations to design, steer and support a multicomponent strategy to address the multidimensional nature of diabetes and other NCDs, in line with the United Nations Sustainable Developmental Goals, World Health Organization (WHO) NCD Global Monitoring Framework, WHO Convention Framework for Tobacco Control and professional practice guidelines, aimed at:

1. Closing the diabetes prevention gap

   We recommend policymakers, planners and managers to implement context-relevant policies through inter-sectoral, inter-department and inter-disciplinary collaborations aimed at:

   - strengthening the educational, environmental, 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 the use of non-physician personnel, assisted by ICT, to implement lifestyle intervention programmes and reduce the risk of T2D in high-risk individuals with linkage to a prepared healthcare system for managing people detected with undiagnosed diabetes and those who have been diagnosed
   - aligning the expectation of care providers, industry and payers to ensure access, affordability and sustainability of the continuing care of people with or at risk of diabetes

2. Closing the diabetes professional knowledge gap

   We recommend universities, accreditation bodies and professional organisations to train knowledge workers as well as funding agencies to support research programmes in the field of diabetes especially in LMICs aimed at:

   - re-designing the curriculum for undergraduates of social, health and medical disciplines to better enable the workforce to provide the acute and long-term healthcare needs of people with or at risk of diabetes and other NCDs
   - 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 healthcare discipline essential for maintaining care standards, translating evidence to practice and providing on-job training
   - promoting research programmes focusing on design, implementation and evaluation of delivery of diabetes care and prevention programmes in a naturalistic environment

3. Closing the diabetes care gap

   We recommend policymakers, payers and planners to increase investments in diabetes care, focusing on prevention of complications, by strengthening the healthcare system aimed at:

- establishing hospital and community-based diabetes centres and teams including professional and non-physician personnel (e.g., trained community health workers/peers) to provide continuing care to people with or at risk of developing diabetes
- ensuring that all individuals with T1D are registered with access to insulin, equipment for self-monitoring of blood glucose and appropriate health education to promote self-management
- re-designing workflow and using 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 (e.g., control of cardiometabolic risk factors, renal function, use of organ protective drugs and self-management) for quality assurance
- leveraging existing facilities and workforce and providing career advancement for HCPs specialised in diabetes to scale up the delivery of data-driven, team-based integrated care

4. Closing the diabetes data gap

   We recommend public health workers, HCPs and researchers, with administrative support, to work collaboratively and use registers, administrative data and audits to complement randomised clinical trials for informing decision-making at patient, providers and system levels by:

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

# 1 Introduction

***By implementing what we have learnt 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***

According to the World Health Organization (WHO), diabetes is diagnosed either by a fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during a 75-gram oral glucose tolerance test (OGTT) and/or glycated haemoglobin ($HbA_{1c}$) ≥6.5% (48 mmol/mol). It is a heterogeneous condition with complex aetiologies, including but not limited to, environmental, lifestyle and genetic factors. The great majority (95%) of affected individuals have type 2 diabetes (T2D), characterised by various combinations of insulin resistance and insulin deficiency. In this document, the term ‘diabetes’ refers to chronic hyperglycaemia fulfilling these criteria irrespective of the aetiologies, unless otherwise stated.

In the last several decades, the scientific community has amassed a large body of knowledge about the growing health and socioeconomic burden of T2D and its multidimensional nature. There is now strong evidence indicating that T2D is preventable and may 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 declining, although there remain major gaps in care, data and outcomes especially in low- and middle-income countries (LMICs). In these countries, insufficient infrastructure and capacity, high costs of medications, fragmentation of healthcare systems, health illiteracy and social disparity are major barriers, resulting in many individuals with type 1 (T1D) or T2D not being diagnosed, treated or managed. Despite increasing healthcare 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 where ageing, poor nutrition and physical inactivity are major drivers. In LMICs, other factors such as environmental pollution, food insecurity and social disparity may also contribute. Once diabetes develops and if not adequately managed, its lifelong nature can have enormous impacts on the individuals, families and society. Given the WHO definition of health as 'a state of physical, mental and social wellness', diabetes is a prime example of how societal factors become major players in disease development which in turn can affect the individuals, families and society.

### *1.1 The Lancet Commission on Diabetes*

In 2016, 26 experts in public health, clinical care, epidemiology and health economics were brought together by The Lancet to 1) review the evidence and knowledge gaps in the field of diabetes, 2) develop strategic and actionable plans ('actions') and 3) estimate the impacts of 'no action' versus 'actions' with a focus on LMICs. In this evidence-based document, 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, which contribute to the lack of provision or poor access to quality preventive care. The consequences are escalating and unsustainable healthcare costs due to complications, which are often preventable in the first place, not only in LMICs but also HICs.

To address these challenges, we have provided a framework where, by redesigning care settings, workflow and team structure, we can implement an integrated diabetes detection, prevention and management plan to reduce incidence of diabetes-related complications and T2D in high-risk individuals. These measures must be supported by inter-sectoral policies in order to mitigate the negative impacts of societal determinants and create long-term benefits. Using epidemiological, clinical trial and real-world data, we have modelled the short- (1–3 year), mid- (10 years) and long-term (20 years) impacts of implementing a multicomponent strategy including societal measures aimed at reducing the burden of diabetes and non–communicable disease (NCD), which will save millions of deaths and billions of dollars in LMICs.

This report provides a data-driven argument for the public, patients, practitioners, payers and policymakers that despite the daunting nature of diabetes and NCD, there are numerous solutions to avert the grave consequences of this global epidemic of diabetes. They will require a collective transformation of our ecosystem and healthcare environment in pursuit of adherence to evidence-based professional guidelines, the WHO NCD Global Monitoring Framework, WHO Convention Framework for Tobacco Control, and United Nations Sustainable Developmental Goals for our society, community and humanity.

## 2 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 (CVD, including mainly ischaemic heart disease and stroke), cancer and respiratory disease, with diabetes increasing the risk of CVD, renal and cancer-related deaths by 1.3–3.0 fold.[1] In 2019, 463 million individuals were affected by diabetes.[2,3] In a worldwide trend analysis, the prevalence of diabetes has doubled in men and increased by 60% in women over the past 25 years.[4] Estimates from the United States of America (USA) and Australia indicate that diabetes reduces life expectancy by at least 6 years when diagnosed at the age of 40 and at least 4 years when diagnosed at the age of 60,[5-7] with childhood-onset T1D having an even greater impact in the absence of adequate care.[8] A 50-year old man in China diagnosed with diabetes at the age of 50 in year 2000 lost on average 9 years of life compared with his peers without diabetes.[9]

According to the WHO, one-third of all global deaths are due to CVD including stroke and ischaemic heart disease. Diabetes confers a 2.3–fold increased risk of CVD[10] while 30% of individuals with

diabetes die from CVD.[11] In less-resourced areas, acute medical crisis such as diabetic ketoacidosis or hyperglycaemic hyperosmolar states remain 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 United Kingdom (UK).[9,12,13] During the recent coronavirus disease (COVID-19) pandemic, patients with diabetes had a 2–5 fold increased risk of severe disease including death compared to those without diabetes, especially amongst those with poor glycaemic control, multiple risk factors or diabetes-related complications.[14,15] Despite the silent nature of diabetes, the COVD-19 global emergency has exposed the vulnerability of these individuals with heavy tolls on healthcare systems, economies and humanity.[16]

### *2.1 Cardiovascular, renal and cancer deaths*

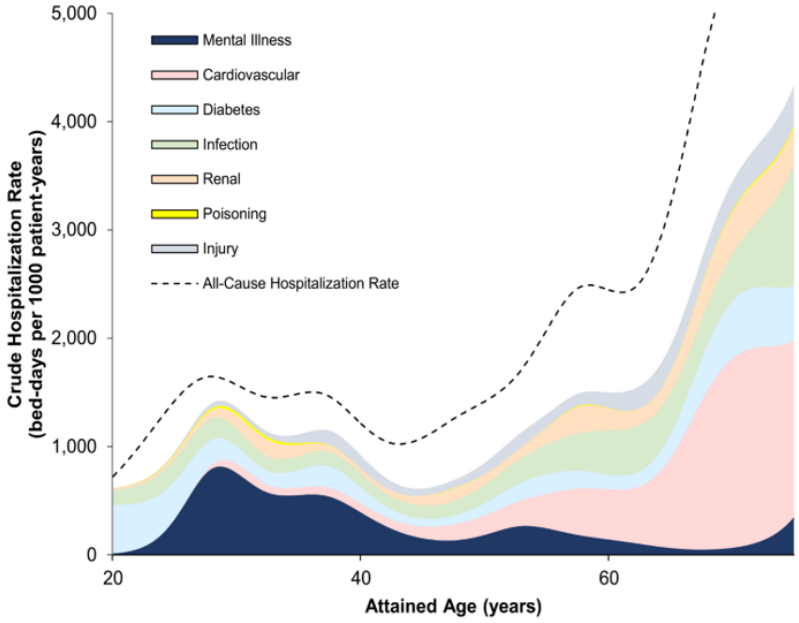
In the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, after accounting for multicausality, 63% of 10.8 (95% confidence interval (CI): 10.1–11.5) million deaths from cardiovascular-renal diseases in 2010 were attributable to the combined effect of high blood pressure (BP), blood glucose, serum cholesterol and body mass index (BMI), compared with 67% [7.1 (6.6–7.6) million] of similar deaths in 1980.[17] In the Global Burden of Diseases, Injuries and Risk Factors Study (GBD 2017), smoking, high systolic BP, high plasma glucose, alcohol use and history of preterm birth in men and, high systolic BP, high plasma glucose and high BMI in women were the leading risk factors in terms of attributable disability-adjusted life years (DALYs).[18] In the USA, the incidence of diabetes-related complications has fallen during the past two decades, but the rate of decline has been much slower for end-stage kidney disease (ESKD) than for CVD.[19] In the US Renal Register, the percentage of ESKD due to diabetes has risen steadily and is presently at around 50%.[20] This rising trend may be due to improved survival from cardiovascular insults in individuals with diabetes, which has given kidney disease more opportunities to evolve.[21]

The high incidence of cancer as a cause of death in people with diabetes was recognised as far back as 1914.[22] With ageing and better prevention of and survival from CVD, there is an increase in this double burden of diabetes and cancer. Even after adjustment for shared risk factors such as age, obesity and smoking, diabetes increases the relative risk for all-site cancer (except for prostate cancer) by 1.2–2.0 fold, as compared with the general population.[1,23] While the mechanisms underlying the close association between diabetes and cancer need further elucidation, the increased risk of cancer in T1D[24] and the independent associations between blood glucose and cancer risk[25] support an important role of dysregulation of glucose metabolism in this risk association. In a recent 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.[26]

### *2.2 Diabetic foot and eye complications*

In a systematic review of 35 population-based studies, with diabetic retinopathy (DR) ascertained from retinal photographs, the overall prevalence was 34.6% for any DR, 7.0% for proliferative DR, 6.8% for 'diabetic macular oedema' and 10.2% for vision-threatening DR.[27] These figures implied an estimated global burden of 93 million individuals with DR and 28 million individuals with sight-threatening stages of DR in 2010.[27] In another systematic review of 8 prospective population-based studies on DR, the annual incidence of DR was 2.2–12.7% with an annual progression of 3.4–12.3%, without sex differences. Although hypertension was not reported as a significant risk factor, suboptimal glycaemic control increased the risk of DR by 10–40%.[28] Individuals with diabetes are 7–30 times more likely to have non-traumatic lower extremity amputations than the general population, accounting for over half of all such amputations.[29,30] Good podiatry care often prevents limb amputation and people who need amputation usually have disseminated vascular disease which contributes to their poor survival rate. In HICs such as North America, Europe and Australia, the incidence of lower extremity amputation among individuals with diabetes has fallen over the past decade.[19,29] The updated estimates of incidence of lower extremity amputation ranged between 1.9 and 3.9 per 1000-person-years in Europe and the USA.[30-32] However, the latest analysis of the national data in USA suggests resurgence of non-traumatic lower extremity amputation in the younger to middle-aged population in recent years.[33]

**Figure 1. Crude hospitalisation rates (bed-days per 1000 patient-years) for selected principal diagnoses, by attained age, among persons with young-onset type 2 diabetes in the Hong Kong Diabetes Register showing the excess burden of hospitalisation and mental illness (Ke C et al Ann Int Med 2019).**




### *2.3 Diabetes, comorbidities and mental health – impact on patients and caregivers*

Individuals with diabetes are twice as likely to suffer from depression than is the general population, a condition often under-recognised and untreated.[34,35] Similarly, individuals with depression are more likely to develop diabetes.[36] Apart from environmental stressors (e.g., socioeconomic deprivation and life events), diabetes and depression may share common behavioural risk factors (e.g., 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.[37] A diagnosis of diabetes calls for changes in lifestyle, long-term use of medications, regular visits to healthcare providers (HCPs) and so on. These demands on day-to-day living may contribute to the high prevalence of anxiety, stress and/or depression, affecting one in 3–5 individuals with T2D.[36] These negative emotions can set up a self-perpetuating cycle of suboptimal self-care and treatment non-adherence, frequent hypo- and hyperglycaemic episodes and poor clinical outcomes.[38,39]

In a recent report using both registers and population-based electronic medical records (EMR) that included 0.42 million Chinese adults with incident T2D observed between 2002 and 2014, data modelling indicated that patients with young-onset T2D (YOD), diagnosed before the age of 40, spent an average of 100 hospital-days from diagnosis to age of 75 with one-third of the hospitalisations due to mental illness before the age of 40 (Figure 1).[40] The frequent clustering of multiple morbidities increases the complexity of the management of T2D. In the UK, using the Clinical Practice Research Datalink, researchers analysed the co-occurrence of 18 chronic conditions, including diabetes, and reported that compared with those living in affluent areas, patients living in the most deprived areas had more comorbidities which frequently clustered with depression especially in women.[41] Using data on demographics, comorbidities and disease duration in patients with T2D, researchers from Singapore reported 5 clusters where clustering of depression in young women with short to moderate disease duration as well as in older patients with moderate to long disease duration and multiple morbidities were the highest tertiary health care users.[42]

Adding to this challenge is the growing burden of diabetes, cognitive decline and dementia.[43] The presence of these comorbidities does not only affect the quality of life of the patients but also markedly increases the emotional burden on the caregivers, which is amplified by poor access and continuity of care and insufficient communication amongst different service providers and specialities. While there are examples of good practice often due to the behaviour of individual physicians, a system-wide approach requiring better communication and care coordination is needed to address the physical and emotional needs of both the patients and their caregivers.[44]

## 3 YOD requires better risk stratification and disease classification

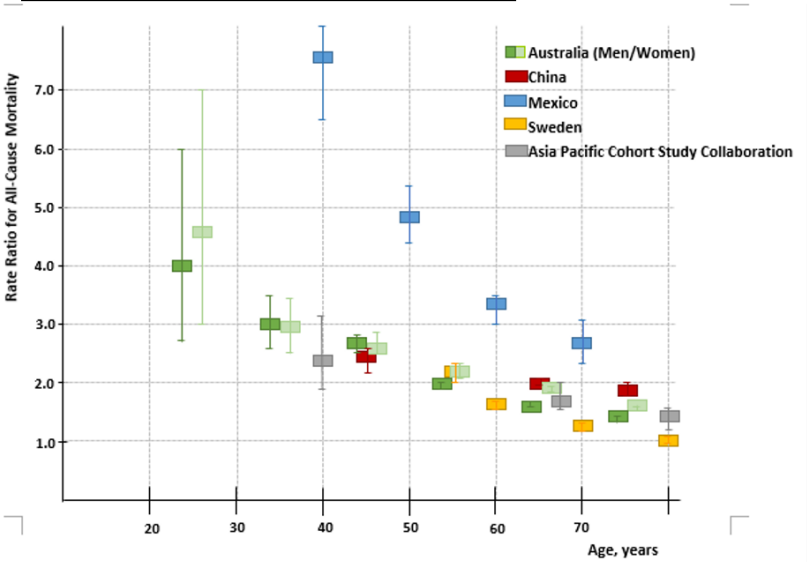
From 1980 to 2014, the global age-standardised diabetes prevalence in adults aged 20 years and older increased from 4.3% (2.4–7.0) to 9.0% (7.2–11.1) in men, and from 5.0% (2.9–7.9) to 7.9% (6.4–9.7) in women. These trends were driven largely by ageing and worsening risk factors, notably obesity, as well as by declining death rates among individuals with diabetes in some countries. During the same period, the age-standardised prevalence in working age (20–64 years) adults 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.[4] In some communities (e.g., Native Americans), there was a rise in total diabetes prevalence in children and adolescents which was mostly attributed to T2D.[45]

### *3.1 YOD increases risk of premature death, morbidities and hospitalisations*

In the early 1970s, Pima Indians diagnosed with T2D before the age of 25 were reported to have high rates of morbidities (ESKD, amputation, blindness) and death after an average of 15–20 years duration of diabetes.[46,47] Similar findings were also reported in Japanese patients with YOD with higher rates of diabetic nephropathy compared with T1D.[48,49] In Hong Kong, the rising incidence of both T1D and T2D in people under the age of 40[50] concurred with the most rapid rate of increase in renal replacement therapy in the 45–65 age group.[51] In the clinic-based Joint Asia Diabetes Evaluation (JADE) Register, 1 in 5 adults with diabetes in Asia had YOD.[52] In a survey of 0.42 million Chinese adults with diabetes under public care, patients with YOD had the highest hospitalisation rates by 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 CVD and 1.7 for infection, compared with their late-onset counterparts.[40]

The high prevalence of complications in YOD is driven mainly by long disease duration.[53] Compared with age-matched individuals without diabetes, the mortality rate ratios are consistently higher in younger age groups, in part due to their low background mortality (Figure 2).[9,12,54] In the USA, a temporal decline in the rates of CVD and related death among older individuals was far less evident in their younger counterparts.[19] In the Swedish National Diabetes Register, patients with T2D diagnosed before the age of 40 had 2–4 fold higher risk of cardiovascular and non-cardiovascular mortality, heart failure and ischaemic heart disease compared with control populations. All these risks were attenuated progressively with increasing age and substantially in those diagnosed after the age of 80.[55] Using data from the National Diabetes Services Scheme between 1997 and 2011 involving 743,709 Australians with T2D, a 10-year earlier diagnosis (equivalent to 10 years' longer duration of diabetes) was associated with a 20–30% increased risk of all-cause death and about a 60% increased risk of death due to CVD.[56] In the Hong King Diabetes Surveillance Database including 770,778 patients with T2D, all-cause and cause-specific death rates had declined by 50–80% between 2001 and 2016. However, in the 20–44 age group, the death rates did not decline with the standard mortality ratio (SMR) fluctuating between 4.92 and 7.89 during the same period.[57]

**Figure 2. Standardised rate ratio (SRR) for all-cause mortality for people with diabetes compared to the general population, according to age and countries (refer to supplemental text for details of references).**




### *3.2 Diagnosing, classifying and managing YOD and other diabetes subtypes*

In the early 1980s, amongst Caucasians, over 90% of patients with diabetes diagnosed young (e.g. before the age of 40) were considered to have classical T1D due to autoimmune islet destruction with acute ketosis and absolute insulin deficiency.[58] In HICs, the tendency to develop ketosis means that patients with T1D are less likely to default the medical system for too long before they present with acute emergencies.[59] However, in non-Caucasian populations including those from Mexico,[60] India[61] and China,[62] classical, ketosis-prone T1D remains relatively uncommon in young adults diagnosed with diabetes. In Chinese patients with YOD, only 10% had classical T1D. In the remaining patients, 60% were overweight and 30% were normal-weight. After 9 years of follow up, overweight patients with YOD had a hazard ratio of 15.3 (2.1-112.4) for CVD and of 5.4 (1.8-15.9) for ESKD while patients with T1D had the lowest event rates.

In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study and the SEARCH for Diabetes in Youth Study in the USA, adolescent-onset T2D is characterised by rapid deterioration in beta-cell function and poor metabolic milieu versus T1D or late-onset T2D.[63] In the TODAY Study, 50% of patients with youth-onset diabetes (10-17 years) treated with metformin monotherapy had treatment failure ($HbA_{1c}$>7.9% [63 mmol/mol] for at least 6 months) during a 4-year follow-up period.[64] Hormonal perturbations during puberty might have contributed to increased insulin resistance and poor glycaemic control.[65] In the SEARCH for Diabetes in Youth Study, researchers reported high BP in 30% and a high LDL-cholesterol in 50% of the non-Hispanic white youths with T2D.[66] In a recent American Diabetes Association position statement, maternal history of diabetes or maternal hyperglycaemia during the child's gestation, family history of T2D, non-Caucasian ethnicity, features of insulin resistance (e.g., polycystic ovary syndrome) and small-for-gestational-age are considered major risk factors for youth-onset diabetes,[67] with the combination of stunted early growth and adolescent obesity being a particularly strong risk factor.[68]

Unlike patients with T1D and adolescent-onset T2D who are often managed in specialist centres by paediatricians, young adults diagnosed with T2D between 18 and 40 years are usually managed in primary care and adult specialist clinics. According to the USA National Health and Nutrition Examination Survey (NHANES), young adults (18–44 years) were less likely to attain a composite $HbA_{1c}$, BP and LDL-cholesterol targets than older adults, and the rates of target attainment had not improved during the 11-year observation period (2005-2008 and 2013-2016).[69] In Asia, despite considerable variations in the attainment of treatment targets across countries, probably reflecting

different quality of the healthcare systems, patients with YOD had consistently worse control of risk factors than their late-onset peers.[52]

Obesity and family history are prominent features in YOD.[70] Despite their non-T1D presentation, patients with YOD often require earlier insulin treatment than those with late-onset disease.[71] In Chinese patients with YOD, 8.1% of patients had glutamic acid decarboxylase antibodies (GADA) suggestive of latent autoimmune diabetes in adults (LADA). While these patients had 60% lower risk of developing CVD, they had greater response to insulin than those without GADA (2.3% versus 0.7% reduction in $HbA_{1c}$), albeit with 60% higher risk of developing severe hypoglycaemia. Compared with patients with classical T1D presentation, patients with YOD and positive for GADA had nearly 3-fold higher risk of ESKD.[72]

The discovery of both common and rare genetic variants including maturity onset diabetes of the young (MODY) due to single gene mutation with high penetrance calls for more precise diagnosis in these young patients. Apart from family screening, identification of these genetic causes have implications for treatment selection with some benefiting from early insulin treatment and others from oral drugs.[73] Adding to this complexity, patients with YOD often have multiple cardiometabolic risk factors, worsened by psychosocial distress[38,74] with poor adherence or frequent clinic defaults.[52,75,76] In a prospective population-based analysis, modelling revealed that by delaying the onset of diabetes or optimising control of all cardiometabolic risk factors, the hospitalisation rates in YOD could be reduced by 30–60%.[40] However, the lack of evidence-based guidelines due to exclusion of these young patients from large randomised clinical trials (RCTs)[77] pose additional challenges in optimising care in these patients. Given their heterogeneous aetiologies, long disease duration and extremely high lifetime risk for life-threatening complications,[59,78] adults with YOD, not dissimilar to T1D, will benefit from inter-disciplinary care in specialist-led diabetes centres for the ascertainment of aetiology (where possible) and intensive risk factor management including lifestyle intervention and psychosocial support, as and when needed.

Indeed, the phenotypic heterogeneity and variable treatment responses are not limited to YOD. In the United Kingdom Prospective Diabetes Study (UKPDS), 12% of adults with T2D had either GADA or islet cell antibodies (ICA) and 4% had both antibodies. These patients with LADA had the most rapid rate of oral medication failure and insulin requirement, especially amongst patients aged less than 45 years.[79] In a multicentre Scandinavian cohort of 8,000 adults with T2D, researchers used GADA, HOMA (Homeostasis model assessment) indices (HOMA %B for beta-cell function and HOMA-IR for insulin resistance, derived from fasting plasma glucose 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 which predict insulin requirement and CKD.[80,81] Using RCT data, other researchers confirmed the prognostic value of these clusters but indicated that the use of specific phenotypes, notably $HbA_{1c}$, age of diagnosis, estimated glomerular filtration rate (eGFR) and BP, outperformed these clusters in predicting treatment responses.[82] Taken together, these findings point to the increasing need to use data more effectively to stratify risk and classify patients in order to personalise care, especially in young patients and those with an atypical presentation.

### *3.3 Abnormal beta-cell biology is a key feature in both T1D and T2D*

Glucose is an important 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 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.[83] While autoimmune destruction of islets is considered the primary event in T1D,[84] abnormal beta-cell biology also plays an important role in T2D. There are considerable inter-individual variations in the weight (0.5–1.2 gram) and number of islets (100,000 to 2.3 million) in humans,[85] with close correlation between BMI and islet mass,[86,87] which are particularly relevant to people living in LMICs such as Africa.

Compared with individuals with normal glucose tolerance, those with impaired glucose tolerance (IGT) had reduced first-phase insulin secretion with compensatory hyperinsulinaemia to correct hyperglycaemia, as well as non-suppression of glucagon during oral glucose ingestion.[88] [89,90] To date, over 400 genomic loci have been discovered in T2D 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 may reflect the overlapping nature of these biological pathways with frequent co-occurrence of obesity, diabetes and other NCDs.[91]

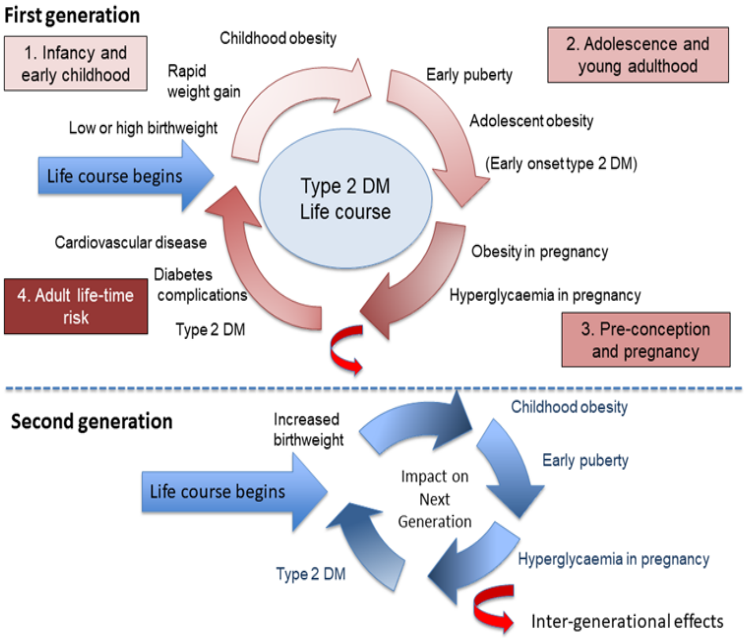
### *3.4 Obesity, maternal hyperglycaemia and perinatal development*

Globally, obesity affected 640 million adults and 110 million children and adolescents in 2014 (10.8% of men, 14.9% of women and 5.0% of children).[92] The prevalence of obesity has doubled in the past three decades, which is mirrored by a similar rising prevalence of diabetes in many parts of the world.[4] Childhood obesity can track into early adulthood and predict ischaemic heart disease in adulthood.[93] The rapid rise in childhood and adolescent obesity may contribute towards the rising trend of YOD and premature NCD, if remedial actions are not taken.[52,94] In a large cohort of Danish men (n=62,565), childhood overweight at 7 year-old was associated with increased risk of diabetes in adulthood only if it continued until puberty or later ages.[95] In the Swedish National Diabetes Register, independent of their countries of origin, those with the earliest onset of diabetes (18–44 years) had a higher BMI, worse cardiometabolic risk factors and a more rapid deterioration in glycaemic control, compared with those with later-onset diabetes.[96]

Epidemiologic evidence for the transmission of diabetes risk to the offspring can be summarised as follows. In the Pima Indian population, risk of developing diabetes was highest in offspring of women with diabetes at conception, followed by offspring of women who developed diabetes after pregnancy, then offspring of non-diabetic women (offspring diabetes prevalence: 45%, 8.6%, 1.4% respectively). Since no increased risk was related to paternal diabetes, these findings highlight the potential contribution of the intra-uterine environment beyond genetic effects.[97]

Data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) follow-up studies showed that offsprings of mothers with untreated gestational diabetes, independent of maternal BMI, had increased risk of obesity and diabetes at age 7[98] as well as increased adiposity at age 10-14.[99] In the SEARCH for Diabetes in Youth Study, participants had a high frequency of parental diabetes and T2D was diagnosed 1.68 years earlier among those exposed to diabetes in utero than among those whose mothers' diabetes was diagnosed later, after adjusting for age of diagnosis of maternal hyperglycaemia, paternal diabetes, sex and race/ethnicity.[99] This is in contrast to paternal diabetes, which was not associated with age of onset of diabetes.[100] In the SEARCH for Diabetes in Youth Study, it was estimated that 47.2% (30.9-63.5) of youth-onset T2D was attributable to maternal diabetes or maternal obesity.[101] Various combinations of high and low birth weight as well as childhood obesity, can result in early age of diagnosis of diabetes. Premature puberty and pregnancy in daughters of mothers with history of gestational diabetes may repeat the same pattern of maternal obesity and hyperglycaemia leading to intergenerational transmission of diabetes (Figure 3).[102]

**Figure 3. Lifecourse development of type 2 diabetes, highlighting the role of different risk factors at different stages of the lifecourse. Adolescent obesity and maternal hyperglycaemia are some of the factors that contribute to risk in the next generation, and perpetuating the rising prevalence of young onset diabetes. There are numerous opportunities for prevention and intervention during the lifecourse. The red curved arrow linking different generations represent a combination of different effects including the effects of maternal hyperglycaemia and obesity (directly via modulating growth as well as through epigenetic mechanisms), altered microbiome, as well as shared genetics and behaviour, environmental exposures (Ma RC and Popkin BM PLoS Med 2017).**




Apart from shared environment, socioeconomic position (SEP) and lifestyles, the unfavourable metabolic milieu starting from pregnancy, along with other external factors, throughout a lifecourse, can affect gene expression (so-called epigenetics) to influence multiple pathways manifested as multiple phenotypes (e.g., obesity, inflammation and beta-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 T2D substantial.[103] Women with maternal obesity and hyperglycaemia are at high risk for developing T2D and CVD. Pregnancy is a great opportunity to influence the future health of mother and child. Integrating maternal and child care including perinatal education and postnatal assessment and advice on individual maternal risks for diabetes can be the first step towards this important goal.[104] Yet, only about 30% of women attend for postnatal glucose testing, which calls for implementation of local strategies to reach most women. User-friendly screening tests such as risk scores, fasting blood glucose and $HbA_{1c}$ can be used to increase the postnatal testing rates in these high-risk women.[105] Taken together, the high prevalence of maternal hyperglycaemia and its potential impacts on future generations, suggest the importance of public health action at early stages of the lifecourse which, by producing results that may go beyond generations, are of far-reaching impact.[106]

## 4 Using 'epidemic' to describe diabetes highlights the importance of environment and behaviour

The word 'epidemic' is often used to describe the global challenge of diabetes. It refers to the phenomenon of 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 (e.g., poor sanitation), an agent (bacteria) and transmission to a susceptible individual (host).[107] Diabetes is a classical example of complex diseases as it has multiple causes, none of which are either necessary or sufficient for disease development.[108] However, the changes in the ecosystem and human behaviour, as prominent features in the current epidemic of diabetes and other NCDs, can be viewed as a complex event due to environment-host interactions, which will require a social-biological strategy.

### *4.1 Ethnicity, socioeconomical development and risk of diabetes and its complications*

Non-Caucasian populations, notably Mexicans, Africans and East Asians, only need a small increase in adiposity to develop diabetes, in part due to insufficient insulin response to compensate insulin resistance associated with weight gain.[89,109] In the USA Multiethnic Cohort, the age-adjusted diabetes prevalence ranged from 6.3% in Caucasians to 10.2% in Japanese, 16.1% in Native Hawaiians, 15.0% in African Americans, and 15.8% in Latinos. After adjustment for other risk factors, the 2-fold higher risk for diabetes amongst non-Caucasians remained in all BMI categories.[110] The marked increase in diabetes prevalence in migrant populations living in modern societies who originated from LMICs, as well as the exponential rise in diabetes prevalence in LMICs with socioeconomic development, highlight the importance of environment-host interactions.[111]

On an individual level, diabetes risk can be further influenced by age, sex, ethnicity, genetics and education level.[3] The impacts of rural-urban migration can be demonstrated in many developing countries. Using India as an example, in a nationally-representative, population-based survey (2012–2014) of 1.3 million adults, the crude prevalence of diabetes and hypertension varied from 3.2% to 19.9% and 18.0% to 41.6%, respectively, with variations by age, state and rural versus urban locations.[112] In another prospective epidemiological survey of 9,848 adults in India, between 2006 and 2016, the most rapid increase in diabetes prevalence occurred in towns (16.4% to 20.3%) and peri-urban villages (9.2% to 13.4%) compared with cities (18.6% to 21.9%), wherein age, family history of diabetes and central obesity were major risk factors.[113]

Given the cross-influence between ecological and biological development, in the early 1990s, anthropologists warned against the potential mismatching between biology and modernisation leading to 'diabetes running wild'.[114] The tendency of non-Caucasians to store fat centrally rather than peripherally contributes to the early development of insulin resistance. Despite their low BMI, this preponderance for visceral fat deposition is often associated with increased lipolysis and inflammatory responses.[115] Many theories have been put forward to explain the global epidemic of diabetes. In the 'capacity-load model', imbalance between 'metabolic load' (e.g., 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 inability to maintain metabolic homeostasis 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 may be particularly relevant to LMICs.[116]

Other researchers have hypothesised that genetic traits and/or phenotypes that promote efficient energy storage and/or activation of the stress and inflammatory responses might confer survival advantages in a food-deprived, physically strenuous and pathogen-rich environment.[117] Thus, people with ancestors who led a subsistent lifestyle may have a phenotype of low BMI closely correlated with beta-cell mass[87] while strenuous physical activity and external stressors such as infections may encourage storage of visceral fat for efficient release of free fatty acids and cytokines. These combined traits of insulin resistance and relative insulin insufficiency may be particularly relevant to populations that undergo rapid nutritional and lifestyle transitions.[62,118,119] To this end, increased activity of the sympathetic nervous system, hypothalamus-pituitary-adrenal axis, renin-angiotensin system (RAS) and innate immunological responses have been reported in T2D. Together with ageing characterised by reduced secretion of growth hormone, insulin-like growth factor 1 and sex steroids which can lead to reduced lean body mass and increased adiposity, multiple subphenotypes including obesity, metabolic syndrome, cardiovascular–renal dysfunction and possibly cancer, all of which share common biological pathways, may emerge.[62,120,121]

### *4.2 Changing demographics, environment and ecosystem*

The demographic ageing transition,[4] along with increasing obesity[92] and physical inactivity,[122] are driving the global epidemic of diabetes. 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 amongst 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 the diet favouring more sugar-sweetened beverages and sodium but with fewer grains, fruits and vegetables, increasing portion sizes and changing work schedules, which in turn alter dietary patterns and sleep schedules. In LMICs, food insecurity, poor affordability for healthy foods (e.g., fresh fruits, vegetables, whole grains) with undernutrition and high consumption of low-quality calories are not uncommon, often made worse by poverty.[111,123] Similarly, in HICs, underserved communities often have limited choices of leisure activities and tend to consume more energy-dense food and often cannot afford healthy foods which tend to be expensive.[124,125] In the latest GBD 2017 analysis, dietary factors explained as much as 20% of the attributable risk of NCD.[126]

Environmental pollutants, many of which are endocrine disruptors, such as bisphenol A, have also been implicated in causing diabetes, obesity and cardiovascular-renal diseases.[127,128] These environmental factors may be particularly relevant in LMICs where the prevalence of obesity is lower than that in Western countries.[129] Other reports have highlighted the impacts of extreme temperature in increasing the risk of CVD events in people with diabetes.[130] Social problems arising from rapid rural-urban migration such as overcrowding, social isolation/disparity and psychosocial stress may 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. While these factors may theoretically contribute to the development of diabetes, more research is needed to quantify the impacts of these societal changes on health and diseases, including but not limited to, diabetes and other NCDs in different populations living in different environments.[13]

### *4.3 Multimorbidity of diabetes including acute and chronic infections in LMICs and underserved communities*

The interactions between chronic infections, notably tuberculosis, and NCDs such as diabetes, are particularly relevant to LMICs such as India, Africa, Mexico, which are hit by these double burdens.[131] Together with the emerging evidence regarding the damaging effects of coronavirus on beta-cells, there is a possibility of worsening of the diabetes pandemic against the backdrop of the COVID-19 pandemic.[132] These two pandemics are likely to hit the LMICs and underserved communities in HICs the hardest. The multimorbidity of diabetes in subpopulations and communities within a socioeconomic and cultural context highlight the considerable heterogeneity of disease predisposition, clinical patterns as well as social and medical needs, which will require a multidimensional strategy.[114]

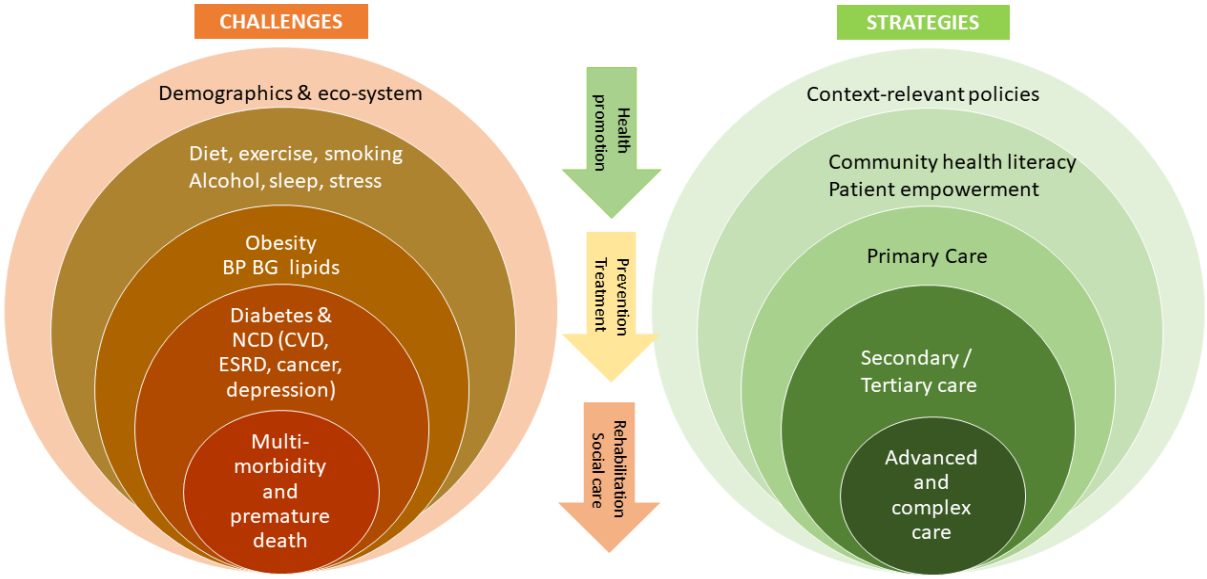
Infections aside, researchers have reported independent associations of obesity, diabetes and CVD with low educational levels and SEP, which contribute towards unhealthy lifestyles.[133,134] In Scotland, in a population-based cohort, life expectancy in people with T2D was reduced at all ages and levels of SEP with loss of 5.5 years in women aged 40-44 in the second most deprived quintile of SEP.[135] In the USA, diabetes-related mortality are closely associated with low-income status, low educational level and non-Europid ethnicity.[136] Within the workforce, long working hours, poor sleep hygiene and shiftwork were associated with increased risk of obesity and diabetes.[137,138] Low education might interact with high personal income to increase the risk of diabetes in population whose affluence has changed recently.[139] In LMICs, the rural-urban migration and social mobilisation especially amongst the young, may be accompanied by other stressors which can lead to risk-conferring behaviours such as the use of tobacco and binge drinking. In China, while high income and high education level were associated with increased risk of diabetes in men, high education level was associated with reduced risk of diabetes with income having little or no effect size in women.[140]

The clustering of these risk factors are further modified by socio-anthropological factors such as geo-physical environment, family SEP, age of migration, levels of acculturation and adaptation to new cultures. Indeed, the social gradient of diabetes in LMICs can be complex. It depends on the specific measure of SEP, as well as the level, speed and pattern of economic development. The gradient may be positive in some countries and for some measures of SEP, can be negative in others,[141-143] where lower SEP may be associated with a more physically-active lifestyle and less access to excess dietary calories. The frequent clustering of diabetes, depression and poverty in LMICs as well as 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 as 'syndemic'.[144,145] The impact of COVID-19 with high rates of death, amongst not just those with diabetes but also certain communities such as African Americans and minor ethnicities, where inequalities, poor access to care, comorbidities often prevail, is a wakeup call regarding the need to protect the vulnerable for common good.[146]

To this end, the recent Lancet Commission Reports on the close links between climate change, food systems and global epidemic of obesity and NCD[147,148] remind us once again of the fragility of human health in a rapidly changing ecosystem,[149] which calls for an integrated socio-biomedical approach to protect health and prevent disease (Figure 4). In recognition of these societal determinants of NCD, in the recent United Nations Health Summit, environmental protection and mental illness have been included as top agenda items in the fight against NCD.[150-152]

**Figure 4: The environment-lifestyle-host interactions underlie the complex nature of diabetes and NCD which requires a combination of personal and societal strategies by using context-relevant policies and system change in order to cover the full spectrum of health promotion, prevention, treatment, rehabilitation, and social care (refer to Table 1 and section 7.1).**




## 5 The healthcare and societal costs of diabetes

The disproportionately higher rate of increase in healthcare expenditure compared with that in Gross Domestic Product (GDP) are in part due to ageing, rising costs of technology and increasing expectation from patients and public. This discrepancy between earning and spending calls for better healthcare planning and more cost-effective use of finite resources.[153] In 2016, global spending on healthcare was USD 10.3 trillion (purchasing power-adjusted) in total or USD 1,400 per capita.[154] The respective per capita healthcare spending has increased at an annual rate of 4.0% from 1995 to 2016. This spending is expected to continue to increase to USD 2,373 per capita by year 2040, at a rate which exceeds the growth of national income.[155]

Around one-tenth of global healthcare expenditure was devoted to the treatment of diabetes, mainly for treatment of its complications and comorbidities. In 2017, the cost of care for people with diabetes accounts for 1 in 4 healthcare dollars in the USA, an average of USD 16,750 which is 2.3-fold higher than for an individual without diabetes.[156] In the USA with predominantly private healthcare, individuals with diabetes and ischaemic heart disease, congestive heart failure, hemiplegia and amputation had 50–70% higher costs, and those with ESKD with renal transplant had 500% higher cost than those without complications.[157] In a recent report from Italy where healthcare is largely publicly-funded, researchers used a simulation model and estimated the average yearly costs per patient with diabetes could rise from USD 382 in those without morbidity to USD 7,937 in patients with coronary,

cerebrovascular, renal and retinal complications.[158] Irrespective of the number of comorbidities, over 70% of the costs were due to hospitalisation. Two-thirds of direct healthcare expenditure was due to treatment of complications, with outpatient care and medications accounting for a smaller proportion of the total costs.

Apart from direct medical costs which include outpatient and inpatient services, emergency care, medications, laboratory tests, medical equipment and supplies as well as long-term care, people with diabetes may have reduced work performance. They may also miss more workdays due to health condition, and their working lives may be cut short by permanent disability and premature death.[159] The productivity loss due to the shorter working lives, sick leave (absenteeism) and reduced work performance (presenteeism) are indirect costs of diabetes. If a large population of young individuals are affected by diabetes which increases the risk of premature death and morbidity, their productive potential will be reduced, resulting in reduced growth of national economies. The loss of earning can lead to a vicious cycle where diabetes aggravates poverty which can worsen access to care, poor outcomes and low productivity.

Individuals in LMICs and to some extent, underserved individuals and their families in HICs, often have low levels of awareness and face greater 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, while some 70% of individuals with diabetes lived in LMICs, more than 90% of the global expenditure was in HICs. There are also enormous variations in healthcare expenditure on diabetes ranging from 2% in Rwanda to 41% in Nauru of a country's total healthcare expenditure.[160] To this end, the 2–3 fold higher and rising incidence of CVD and death rates in LMICs (e.g., India) as compared with the declining rates of CVD in North America and Europe suggested the need to invest more in preventive care in LMICs, which have the least affordability to pay for expensive treatment for late complications.[40]

In 2015, the estimated global indirect cost of diabetes was USD 294 billion or 35% of the total economic burden of diabetes. Of the total indirect cost, 94% was due to either premature death or dropout from employment due to disability. In LMICs, over 64% of indirect cost was from premature death and 60% in HICs. Individuals with diabetes in LMICs tend to die at a younger and productive age than their counterparts in HICs.[161] The global economic burden of diabetes is expected to increase due to the growing population of diabetes and the increase in per capita medical expenditure for diabetes. The projected total global economic cost due to diabetes was predicted to increase from USD 1.3 trillion (1.8% of global GDP) in 2015 to USD 2.2 trillion (2.2% of global GDP) in 2030. The direct medical cost would increase from USD 0.86 trillion to USD 1.70 trillion, while the indirect cost would increase from USD 0.46 trillion to USD 0.78 trillion.[162]

From a value perspective, the substantial amount of resources used to treat diabetes and its complications could be used for other productive activities including diabetes prevention measures.[163] Some studies have simulated the impact of diabetes on GDP at the country level or globally. Predictions have shown that global GDP might have been USD 1.7 trillion higher from 2011 through 2030 if diabetes had been eliminated in 2010. While such losses would be borne largely by HICs (53% of total), the predicted GDP loss for China was USD 49 billion and for India was USD 15 billion.[161] Another study estimated that Finland's GDP would be 1.1% higher if diabetes were eliminated.[164]

## 6 Access to care, education and medications in T1D

In HICs, the major current focus in T1D is on reducing the treatment gaps in the prevention of micro/macrovascular complications as the leading cause of death.[165] The situation is far worse in LMICs where poverty and lack of infrastructure and professional knowledge often lead to limited insulin availability with poor access to diabetes education. As a result, children with T1D often have an extremely poor outlook, they are frequently misdiagnosed, develop acute and chronic complications, and die prematurely.[166-168] Competition between manufacturers has led to the availability of relatively

inexpensive insulin products, which should be part of the essential medicines list in all LMICs as recommended by the WHO and made affordable and available with appropriate use.[166,167,169,170]

### *6.1 Ensuring access to insulin and patient education to improve self-management*

A particular concern for those with T1D is the high level of training needed for HCPs, not just physicians but also nurse educators, dietitians and social workers. In turn, tailored diabetes education of patients and relevant family members is important, covering not just insulin and self-monitoring of blood glucose (SMBG), but also diet (preferably with carbohydrate counting), exercise and other factors.[171] Attention needs to be given to the time at school for children, addressing stigma, managing 'sick days', as well as dealing with issues of adolescence including contraception and pregnancy planning. Education materials should be culturally sensitive and written accessibly. The period of transition of a young individual to adulthood with utilisation of adult healthcare services is a pivotal time that needs locally-adapted and effective programmes.[172] Monitoring and benchmarking efforts are key to achieving improved care, and international benchmarking efforts are available. By highlighting different outcomes between clinics in similar situations, this can provide the impetus for improving the organisation and quality of care.[173,174]

Insulin analogues are now widely used in many countries. Basal insulin analogues are better than human or animal (bovine and porcine sources) insulins for minimising the risk of nocturnal hypoglycaemia and are particularly useful for basal-bolus regimens (multiple daily injection therapy involving a long-/intermediate-acting insulin and short-/rapid-acting insulin at each meal).[175,176] That said, human and biosimilar insulins are more affordable insulins in low-income areas.[177,178] In T1D, basal-bolus insulin regimens offer better glycaemic control than twice-daily regimens, if accompanied by appropriate education of individuals with diabetes, family and care providers with access to adequate supplies of needles, lancets and testing strips for performing SMBG. However, the cost of SMBG is often higher than that of insulin.[179] In some LMICs, the tariffs on insulin and SMBG supplies often reduced the affordability of these treatments.

Many clinics are still using twice-daily insulin regimens, often with premixed insulin.[166] These regimens are usually associated with higher $HbA_{1c}$ and more frequent hypoglycaemia, especially when used with little or no SMBG and diabetes education, although other non-insulin determinants of quality of glycaemic control are also important.[180] In these settings, we have observed that due to limited insulin, food insecurity, unavailability of SMBG and glucagon (to reverse hypoglycaemia) and lack of transport and emergency services, there is a tendency to reduce the dosages of premixed insulins. All these factors can increase the risk of poor glycaemic control and complications which can adversely affect growth and quality of life.[172] Even in HICs, poverty, varying healthcare financing or insurance policies, lack of price transparency, complexity in supply chains and insufficient competition amongst a few manufacturers have made insulin and SMBG supplies difficult to afford.[181,182]

### *6.2 Use Diabetes Centres to build capacity and improve care standard in T1D*

The global impact of T1D can be diminished through more 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, healthcare providers must be taught how and when to measure blood glucose in sick children (to prevent death from misdiagnosis) and habituated to doing so as a matter of routine.[168,172,180,183] The establishment of Specialised Diabetes Centres or regional T1D Centres in LMICs provide a focal point for building capacity to improve management of acute emergencies and complex problems (see also Section 9.7). Extra support may 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-hour emergency advice. Peer support also offers potentially profound advantages. While models of care should be adapted to each country's available resources and healthcare system, they should aim to provide at least 'Intermediate Care' as per the 'Levels of Care' (Panel 1), either at no cost to patients, or at a cost affordable to all.[180]

In some countries, programmes such as the Life for a Child,[184] Changing Diabetes in Children[185] and Insulin for Life[186] with in-kind support from pharmaceutical industries and expert volunteers, have

significantly improved care and outcomes.[167] Patient and family education resources such as videos, graphic novels and Conversation Maps (an innovative facilitator-guided group education tool which uses maps to help patients come to terms with living with diabetes) simplified treatment guidelines, while two African training colleges for paediatric endocrinologists are now available. However, many of these programmes are supported by one-off philanthropic donations. Improvement of health systems within countries could provide a more sustainable support system that could have long-term benefits on the health outcomes of children with T1D.

### *6.3 T1D Registers reveal a secular improvement, but with major care gaps*

Although many registers of childhood-onset T1D exist, documentation of the overall burden arising from T1D remains incomplete. There are two main deficiencies. Firstly, incidence and prevalence data from many parts of the world, notably Sub-Saharan Africa, are very limited. Secondly, few studies have focused on adult-onset T1D. The incidence of childhood-onset (<15 years of age) T1D was extensively reported in the landmark DIAMOND study, initiated by the WHO in 1990. The report included data from 112 registers in 57 countries and suggested a 400-fold variation in annual incidence, ranging from 0.1 per 100,000 (China and Venezuela) to 40.9 per 100,000 (Finland).[187] Some of this difference may be due to lack of recognition of cases in less-resourced countries, but up to 30-fold differences in incidence have also been observed amongst HICs, e.g., between Finland and Japan.[3]

However, 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 those aged 10–14 years. There was a male preponderance in high-risk countries and a female excess in low-risk countries. In European countries, incidence had risen by about 3% per year from 1989 to 2003,[188] although this rise appears to be slowing in high-risk countries like Finland,[189] Norway[190] and amongst non-Hispanic whites in the USA.[191] These trends are in contrast to low-risk countries and populations like China,[192] Korea[193] and amongst Hispanics in the USA,[191] where higher rates of increase were seen. Striking increases in apparent incidence may also occur in lower-income countries in part due to increased ascertainment as care improves.[168] In 2017, the International Diabetes Federation (IDF) estimated there were 1.1 million children and adolescents aged less than 20 years with T1D.[3] In adults, the few studies available suggest that, although the incidence of T1D was somewhat lower than that seen in adolescents, it continued to occur throughout adulthood. In Sweden, the incidence of T1D fell from 37 per 100,000 before age 20 years to 27 per 100,000 thereafter, and the rates for those aged 70–79 were higher than for those aged less than 9 years.[194] These findings underscore the importance of more extensive data and studies of T1D in adults despite the difficulties in typology (classification), which is a significant barrier without extensive laboratory testing.

The burden of T1D reflects not just its prevalence and management requirements but also the consequences of the long-term risk of major complications (visual loss, foot ulcers, CVD, lower extremity amputation, diabetes-related death) (Figure 5A). These data are from the Pittsburgh, Pennsylvania (USA)-based Epidemiology of Diabetes Complications (EDC) study. After 30 years of exposure to hyperglycaemia, nearly 80% of patients with T1D suffered one or more of the above complications. Although visually, the bar charts suggest declining incidence of complications across the different cohorts, none of these trends were significant indicating no improvement in these complications rates overtime. These data highlight the urgent need to further improve clinical management, particularly for hypertension, as reported in another EDC subanalysis.[195]

In HICs such as Australia, the death rate in patients with T1D is less than 2 per 1000-person-years. By contrast, recent reports from Africa and Central Europe indicate that rates are 9 or more fold higher (Figure 5B). In the USA and Europe, and in places like Taiwan which generate high-quality national data, life expectancy of patients with T1D has improved over time, although an individual with T1D may still lose up to 17 years of life compared with the general population.[196] To put this figure into perspective, patients diagnosed 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 these HICs, such improvements have not been seen in LMICs. A loss of 28 years of life was estimated in Mali in the early 1990s.

On the other hand, social disparity remains a major barrier to care in HICs. Between 1979 and 1984, among African Americans in the USA, T1D was associated with 30 years loss of life expectancy as compared with 20 years loss in the general population.[197] Although the survival rates have improved in recent years, the gap between African Americans and the general population persisted.[165] In Scotland, from 2006-2010 to 2011-2015, the age-standardised mortality rate per 1,000 person-years in people with T1D had declined from 24.8 to 20.4 in men and from 22.5 to 17.6 in women. However, during the same period, the rate ratios for the most versus least deprived groups had increased from 2.49 to 2.81 in men and from 1.92 to 2.86 in women.[198] These marked variations in T1D survival over time between countries and within countries highlight the impact of national socioeconomic development and social/care disparity on clinical outcomes, even in HICs.[199-201]

**Figure 5A. Cumulative incidence of diabetes-related complications and related death within the examined Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort of childhood-onset type 1 diabetes, according to calendar year of diagnosis. The p values highlight the lack of improvement of these trends within each age group diagnosed during different time periods.**

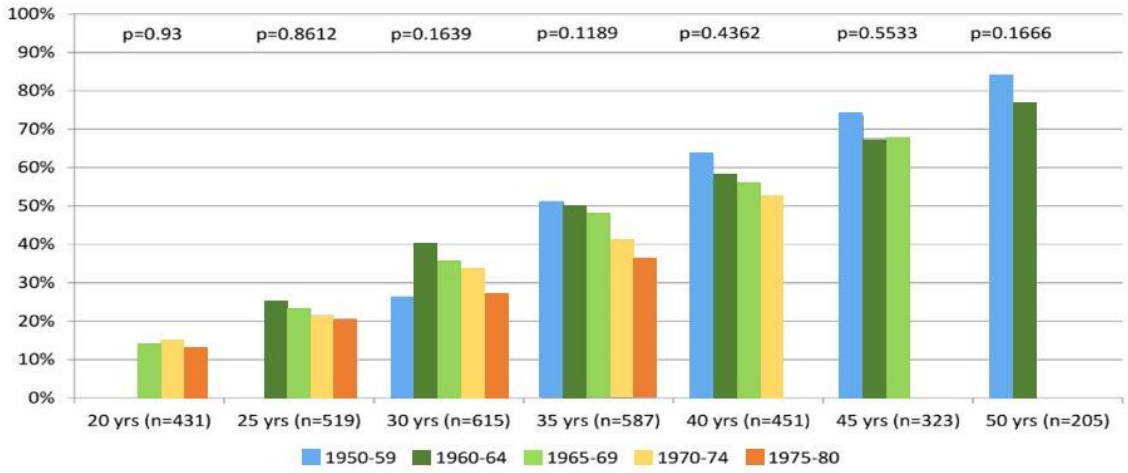
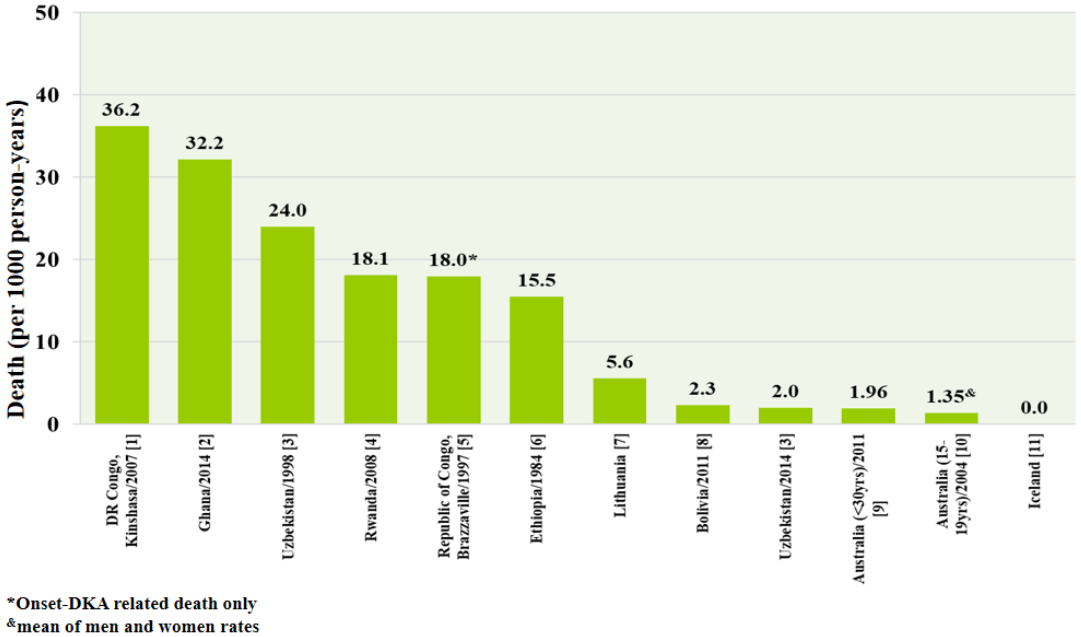



**Figure 5B. Premature death in patients with type 1 diabetes diagnosed before the age of 40 years in different countries (refer to supplemental text for details of references).**




*Onset-DKA related death only
&mean of men and women rates

### *6.4 Standardised mortality ratio and excess deaths in young individuals with T1D due to care gaps*

In HICs, quality care (defined as 'guideline-based comprehensive' care) is generally provided to young individuals with T1D. In contrast, most young individuals in low-income, low-to-middle-income and many young individuals in upper-middle-income countries receive 'minimal' or 'intermediate' care (Panel 1).[180] We estimated the excess mortality due to this care gap in individuals aged less than 25 years and diagnosed with T1D before the age of 20. This was done by searching the literature for mortality data in young individuals with T1D diagnosed during childhood or youth, wherein the SMR was stated or could be calculated by comparing the stated mortality rate to background mortality using the WHO lifetables data. Eighteen studies were identified on comprehensive care from HICs, three on intermediate care from upper-middle-income countries, seven on intermediate care from lower-middle and low-income countries (pooled), and one each on minimal care from lower-middle and 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, estimated SMR 13.6) and low-income countries (50% minimal and 50% intermediate, estimated SMR 33.9).

Using incidence data of T1D from the IDF, population data and background mortality rate from the United Nations,[202,203] as well as age of diagnosis reported in different studies, we developed a discrete time Markov illness-death model[204] with age-dependent transition probabilities for all 220 countries listed in the IDF Atlas. We estimated that globally 14,466 young individuals with T1D died in 2017, from a total prevalence of 1.61 million. If all patients in LMICs received an intermediate level of care with reduced SMR, 8,369 deaths could have been averted (58% of all deaths). This number increased to 12,092 if all nations were to implement guideline-based comprehensive care resulting in a further reduced SMR (84% of all deaths averted) (refer to Supplemental Material).

## 7 Reduce diabetes-related complications by reducing multiple risk factors

In the last three decades, prospective cohort analyses have reported the risk associations of BP, blood glucose, LDL-cholesterol with CVD and death in T2D.[205-207] This was followed by large-scale RCTs which demonstrated that sustained reduction of these risk factors for 2–5 years could substantially improve clinical outcomes in T2D. Subsequent meta-analysis of these RCTs results confirmed that reduction of $HbA_{1c}$ by 0.9% (10 mmol/mol),[208,209] systolic BP by 10 mmHg[210] and LDL-cholesterol by 1 mmol/L (39 mg/dL)[211] individually reduced the risk of CVD and/or all-cause death by 10–20%, independent of other risk factors. In a meta-analysis, it was estimated that for every 200 patients with T2D treated for 5 years, 14 events of myocardial infarction can be prevented with reduction of 4 mmHg in systolic BP, 8 events with 1 mmol/L (39 mg/dL) reduction in LDL-cholesterol and 3 events with 0.9% (10 mmol/mol) reduction in $HbA_{1c}$.[208] Given the important role of activation of RAS[212] in causing cardiovascular-renal diseases, landmark studies have also confirmed the protective effects of RAS inhibitors (RASi) in both T1D[213] and T2D,[214-216] especially in the presence of increased albuminuria.

### *7.1 Use multifactorial management to achieve multiple treatment targets*

Several RCTs have examined the control of multiple risk factors on cardiovascular-renal events and all-cause death, such as the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care), Steno-2, J-DOIT3 (Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases) and SURE (Structured Versus Usual Care on Renal Endpoint in Type 2 Diabetes) trials. In the ADDITION trial, individuals were actively screened for T2D 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.[217] In the Steno-2 Study, multifactorial management including lifestyle intervention; control of blood glucose, BP and LDL-cholesterol; as well as use of RASi and aspirin (as appropriate) in patients with T2D and microalbuminuria without a history of cardiovascular-renal diseases, reduced micro/macrovascular complications after 7.8 years. This translated into a long-term reduction in ESKD and all-cause death,

10–20 years after completion of the trial.[218,219] The number needed to treat (NNT) was 5-8 for death from any cause, death from cardiovascular causes, myocardial infarction and stroke over 13 years. The NNT for amputation was 10.[218] Subsequent economic analysis confirmed the cost-effectiveness of this multifactorial intervention when implemented in a primary care setting.[220]

In the SURE study involving patients with T2D and CKD, after receiving 2 years of team-based care with predefined processes aimed at controlling multiple risk factors, the structured care group were 3-fold more likely to achieve multiple treatment targets with persistent use of RASi than the usual care group. After just 2 years, patients who attained 3 or more treatment targets had 50% reduction in ESKD and all-cause death compared with usual care.[221] Similarly, analysis of real-world databases has indicated the proportional and additive benefits of controlling $HbA_{1c}$, BP and LDL-cholesterol on reducing cardiovascular-renal diseases in T2D, with LDL-cholesterol lowering by statins having the greatest effect size.[222-224] In the latest analysis of the Swedish National Diabetes Register involving over 200,000 patients with T2D, there were linear relationships between the number of cardiometabolic-renal-behavioural risk factors attained (defined as $HbA_{1c}$<7.0% [53 mmol/mol], BP<130/80 mmHg, LDL-cholesterol<1.8 mmol/L (70 mg/dL), lack of smoking and microalbuminuria) and cardiovascular events and related death.[225,226]

### *7.2 Stratify risk to maximise benefits and minimise harm of blood glucose lowering*

In the UKPDS started in 1977,[227] achieving an $HbA_{1c}$ difference of 7.9% versus 7.0% (63 versus 53 mmol/mol) in T2D with conventional and intensive glycaemic control strategies respectively and similarly, that of 9.0% versus 7.0% (75 versus 53 mmol/mol) in T1D in the Diabetes Control and Complication Trial (DCCT) started in 1983,[228] reduced the risk of microvascular complications in the short-term and cardiovascular complications in the long-term. Post-hoc analysis identified the close relationship between $HbA_{1c}$ and diabetes-related complications which provided the premise for the conduct of three landmark studies in 2000, which aimed to achieve lower $HbA_{1c}$ values than seen in the UKPDS and DCCT studies.

In all three trials, namely ACCORD (Action to Control Cardiovascular Risk in Diabetes),[229] VADT (Veterans Affairs Diabetes Trial)[230] and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trials,[231] the majority of participants were over the age of 60, had over 10 years of diabetes with multiple risk factors and complications. All three trials had similar design and outcome measures and an achieved mean $HbA_{1c}$ of 6.4%-6.9% (46-52 mmol/mol) during the trial period. Although all three trials confirmed reduced risk of microvascular complications in the intensively-treated group, the results for cardiovascular death were controversial with premature discontinuation in the ACCORD study due to unexpected increased risk of death in the intensively-treated group. This has triggered intensive research which highlighted the high risk of hypoglycaemia in patients with multiple morbidities especially CKD after long disease duration. The silent deterioration of renal function coincides with progressive atherosclerosis in patients with long disease duration. The frequent coexistence of CVD and CKD put these patients, who often receive complex therapies, at high risk of hypoglycaemia which may precipitate CVD or identify patients with a 'frail' phenotype.[232-234] These observations have led to the changes in practice guidelines calling for regular assessment of risk factors and complications for individualisation of treatment targets and strategies in blood glucose lowering, taking into consideration the demographic, biomedical, cognitive, psychosocial and behavioural profiles of patients in order to maximise benefits and minimise harm.[235-237]

### *7.3 Use blood glucose lowering drugs effectively - old versus new drugs*

Together with insulin first discovered in 1922, metformin and sulfonylurea (SU) discovered in the mid-1950s, have been the standard blood glucose lowering drugs which are effective, albeit not without side effects. On average, except for insulin which can lower blood glucose considerably, most of these medications reduce $HbA_{1c}$ by 0.5 to 1% (5.5-11 mmol/mol) although there are considerable inter-individual variations for a single drug, depending on other factors pertinent to hosts and settings.[238] Patients with high $HbA_{1c}$ often have the greatest response, in part, by ameliorating the effects of glucotoxicity on beta-cell function. However, these patients also have the most residual glycaemic burden requiring additional interventions.[239] Using data from long- and short-term trials, researchers

have reported strong correlations between cumulative glycaemic exposure and clinical outcomes, as well as between differential glycaemic exposure and cardiovascular risk reduction. Thus, if blood glucose lowering could be initiated early and sustained with low risk of hypoglycaemia, long-term benefits should ensue even with traditional drugs such as metformin and SU,[240] as indeed reported by the UKPDS.[227]

Insulin and SU have potent blood glucose lowering effects but can cause significant hypoglycaemia which may lead to hospitalisations,[233,241,242] morbidity and premature death, especially in patients with frailty and multiple morbidities.[243] This has led to the emphasis of periodic assessments and education to deliver patient-centred, individualised care, taking into consideration the risk of hypoglycaemia, comorbidities, obesity and economics. During the last three decades, the pharmaceutical industry has invested heavily to develop new medications to lower blood glucose 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.[244] Suffice to say, this diversity reflects the complex regulation of glucose homeostasis involving multiple pathways which have led to the development of a large number of blood glucose lowering drugs with different extra-glycaemic effects.

Amongst different classes of drugs, the cardiovascular-renal protective effects of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP1-RA), independent of blood glucose lowering, have now been confirmed, giving us additional armamentarium in managing these high-risk patients.[245] However, the high price of these new medications have limited their affordability in low-resource settings. Meanwhile, the efficacy, safety and low cost of metformin as well as the cardiovascular safety of SU when compared with dipeptidyl peptidase-4 inhibitors (DPP4i),[246] have reassured the community regarding the clinical value of metformin and SU that are widely used in LMICs.[247] As new medications such as SGLT2i, DPP4i and GLP1-RA become more affordable, the landscape of use of blood glucose lowering drugs may change, considering their organ protective effects, glycaemic durability and long-term cost-effectiveness.[248] In this light, young patients who face decades of hyperglycaemia with high risk of developing complications during their mid-age[53] warrants special consideration. In these young patients, delaying the onset of diabetes and intensifying glycaemic control using drugs with low risk of hypoglycaemia and weight gain may benefit most from these new medications, although evidence from RCTs is needed to inform treatment guidelines.[77]

### *7.4 Diagnose and treat early to induce diabetes remission and improve glycaemic durability for better outcomes*

Reduced early phase insulin secretion and non-suppression of glucagon[88] followed by progressive decline in beta-cell function[249] is a hallmark in IGT and T2D. In the UKPDS, age of diagnosis, obesity (general and central), baseline plasma glucose and triglyceride were predictors of progressive beta-cell failure and treatment escalation.[250] In a proof-of-concept study, researchers have reported sustained recovery of insulin secretion at 2 years after 2 weeks of intensified insulin treatment in T2D.[251] In the Diabetes Remission Clinical Trial (DiRECT), a primary-care led weight management programme involving patients with T2D with less than 6 years of disease and a BMI of 27-40 kg/m$^2$ (mean BMI 35.1 kg/m$^2$), 149 were randomised to receive intervention with severe and structured dietary restriction and 149, usual care. At year 1, 46% in the intervention group had diabetes remission (defined as $HbA_{1c}$<6.5% [48 mmol/mol] without medications) and 24% had at least 15 kg of weight loss. Amongst patients with weight loss of 15 kg or more, 85% had diabetes remission. At 2 year, 17 (11%) in the intervention group and three (2%) in the control group had weight loss of at least 15 kg, whilst 53 (36%) in the intervention group and five (3%) in the control group had diabetes remission. In a post-hoc analysis of the whole study population, of those participants who maintained at least 10 kg weight loss (45 of 272 with data), 29 (64%) achieved remission; 36 (24%) of 149 participants in the intervention group maintained at least 10 kg weight loss.[252] Using arginine stimulation test, patients who had diabetes remission exhibited similar peak and first insulin response compared with individuals with normal glucose tolerance, suggesting restoration of beta-cell function after significant weight reduction.[253] Despite these encouraging results, the sustainability and long-term impact of intensive weight loss interventions on remission needs continued study.

Although many patients with diabetes have obesity, some are non-obese[254] in whom early amelioration of glucotoxicity may improve glycaemic durability. In the VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) Study, researchers compared the strategy of early intensive treatment using combination therapy of metformin plus DPP4i versus metformin monotherapy in newly-diagnosed patients with T2D in reducing the likelihood of primary and secondary treatment failure. In this 5-year study involving 2,001 patients with T2D who had a disease duration of 3 months and a mean $HbA_{1c}$ of 6.7% (50 mmol/mol) and mean BMI of 31 kg/m$^2$, combination therapy reduced the risk of poor glycaemic control ($HbA_{1c}$>7% [53 mmol/mol] on 2 occasions 3 months apart) by 49% compared with monotherapy. The time to poor glycaemic control was 36 months in the monotherapy group compared with 61 months in the combination group. With early intensified treatment, these patients were 27% less likely to require insulin therapy compared with the monotherapy group who subsequently also received DPP4i.[255]

The glycaemic legacy effect of early intervention in newly-diagnosed patients in UKPDS[227] and individuals with IGT in a diabetes prevention programme[256] has led to long-term reduction of cardiovascular-renal events and all-cause death. Together with the results from DiRECT and VERIFY studies, the use of a system-wide strategy to diagnose and treat patients with T2D early and intensively may induce remission or maintain glycaemic durability with long-term benefits in addition to the use of other medications for organ protection.

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

In addition to smoking, BP, LDL-cholesterol, $HbA_{1c}$ and body weight are amongst the most modifiable risk factors in diabetes. However, the latter two require considerable behavioural changes and self-management. The results of the DiRECT study led by primary care physicians indicated that significant weight reduction with discontinuation of multiple medications is possible,[257] if patients are given adequate support and supervision. While these results are extremely encouraging, many patients with T2D have long disease duration or poor beta-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 aetiologies of T1D and T2D, once 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 depending on disease stage and treatment.[258] Without proper professional training and structured patient education and support, patients and HCPs alike, will find it difficult to explain these blood glucose fluctuations and take corrective actions. Patient dissatisfaction and distress can lead to frustration and burn out for HCPs resulting in poor patient-provider relationships, which in turn may worsen treatment adherence and quality of care.[35,39,259] Training of HCPs in psychological health and behavioural science will help them design, implement and evaluate patient empowerment programmes needed to promote self-management.[260]

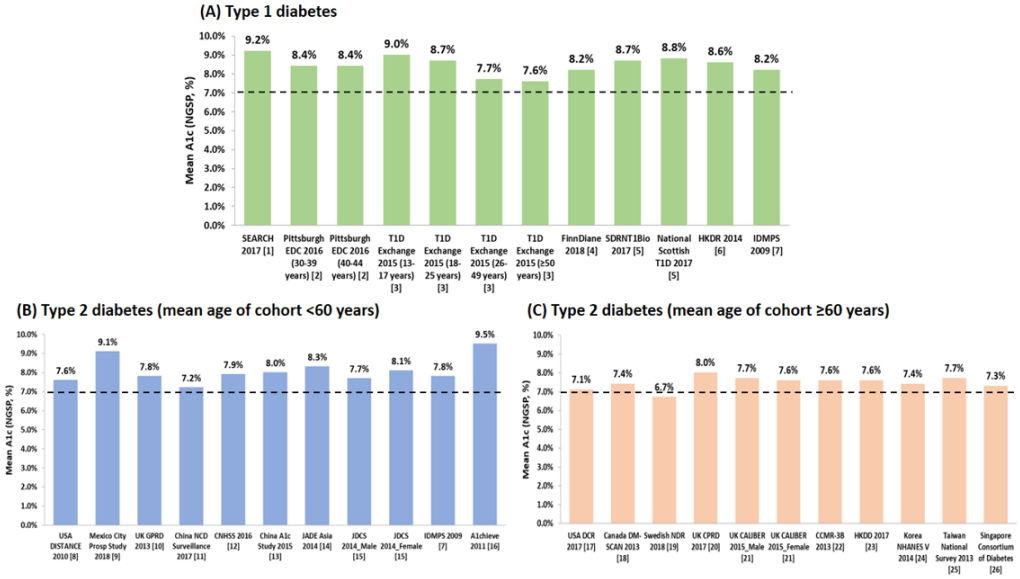
In the UKPDS, after the initial reduction of 2%, there was a progressive upward drift of $HbA_{1c}$,[261-263] in part due to ongoing glucolipotoxicity with progressive beta-cell dysfunction.[264,265] These finding have been confirmed in large-scale surveys of T2D showing loss of glycaemic control over time.[250,266] Similarly, BP tends to rise with increasing disease duration.[266] Ageing aside,[267] lack of regular monitoring, medication non-adherence and delayed treatment intensification all contribute to progressive loss of control of these risk factors in T2D in real-world practice.[268] In several surveys, fewer than 50% of patients had their treatment intensified, even though they had been suboptimally managed for more than 7 years.[269,270] On the other hand, 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.[271,272] In a meta-analysis, after an initial fall 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. The researchers estimated that an average of 23.5 hours of contact time during a 12-month follow-up period was needed to sustain a 1% (11 mmol/mol)

reduction in $HbA_{1c}$.[273,274] By re-organising care, using non-physician personnel and technology,[275] we can improve the efficiency of care delivery to address the psychosocial and informational needs of patients and improve self-care and treatment adherence, especially in those who have not yet developed complications and may have low motivation to change their habits.[276]

### *7.6 Variations in quality of care and clinical outcomes mean control of diabetes is achievable*

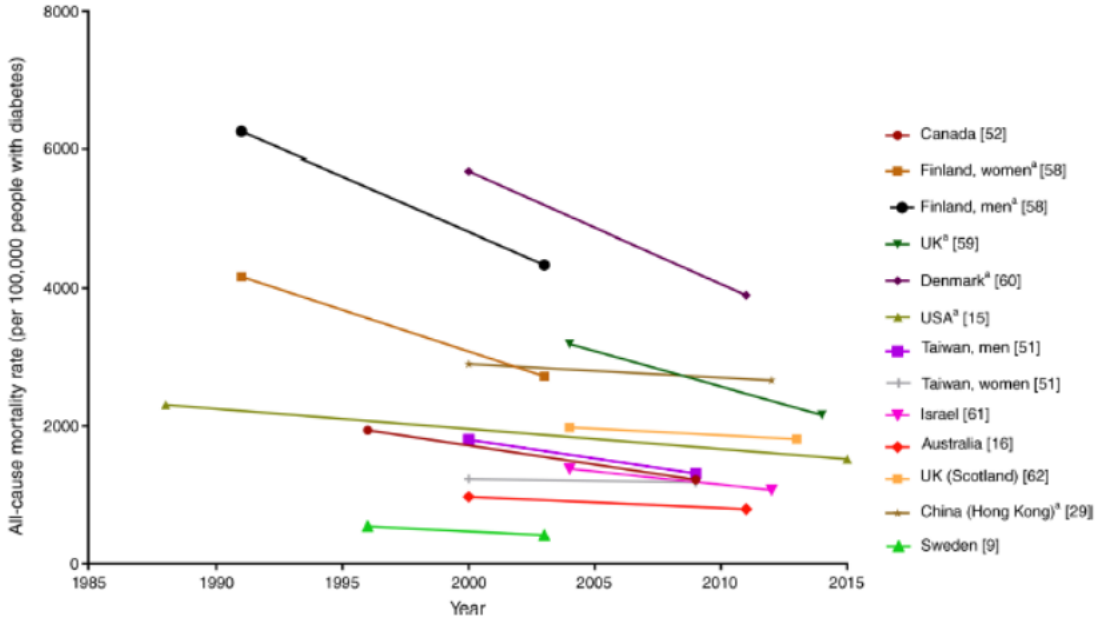
In a 12-year survey consisting of seven waves of patients with T2D, totalling 66,088 recruited by 6,099 physicians from 49 countries outside North America and Western Europe, the proportions of patients with $HbA_{1c}$<7.0% (53 mmol/mol) decreased from 36% to 30.1% between 2005 and 2017.[277] In another multicentre survey involving 10,000 patients from outside the USA and Europe, only 20–30% of people with T2D attained recommended $HbA_{1c}$ (<7.0% [53 mmol/mol]), BP (<130/80 mmHg) and LDL-cholesterol (<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 RASi, or underwent periodic eye and foot examination and blood/urine testing in accordance with international recommendations.[278] By curating data from 40 surveys consisting of 1.9 million individuals recruited from HICs and LMICs with each study enrolling at least 5,000 patients with either T1D or T2D, only 20–40% of individuals achieved $HbA_{1c}$<7% (53 mmol/mol)[247] with worse glycaemic control in patients with T1D and young patients with T2D, highlighting our failure to translate evidence to benefit the larger community (Figure 6).

**Figure 6. A global landscape of $HbA_{1c}$ in 1.9 million people with type 1 or type 2 diabetes reported in more than 20 cohorts with at least 5000 patients per cohort showing high levels of $HbA_{1c}$ especially in patients with type 1 diabetes and young-onset type 2 diabetes (refer to supplemental text for details of references).**




In HICs where access to care, education and medications are covered by either general government funding or public/private health insurance schemes, there have been notable improvements in terms of risk factors, complication rates and health services utilisation (Figure 7). In the USA, between 1990 and 2010, the declining rates of acute myocardial infarction events, death from hyperglycaemic crisis, stroke, lower extremity amputation and ESKD were 67.8%, 64.4%, 52.7%, 51.4% and 28.3%, respectively. The reduction in vascular and renal outcomes was greater in individuals with diabetes than in those without diagnosed diabetes.[19] During the same period, attainment of $HbA_{1c}$, BP, LDL-cholesterol 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 improvements in foot examination and annual serum lipid measurement, and smaller improvements in annual eye and dental examinations.[279,280]

**Figure 7. Trends in all-cause mortality among people with diabetes between 1988 and 2015, by country/region. Note these data are from HICs, showing a paucity of similar data in LMICs (Harding JL et al. Diabetologia 2018).**




In the latest analysis of the Hong Kong Diabetes Database, a territory-wide register of 338,900 Chinese patients with T2D who underwent structured assessment (eye, feet, blood and urine) every 2–3 years in publicly-funded healthcare institutions with access to education and medications, there were significant improvements in risk factor control and increased use of statins and RASi between 2002 and 2012. The proportion of patients achieving $HbA_{1c}$<7% (53 mmol/mol) increased from 32.9% to 50.0%, BP≤130/80 mmHg from 24.7% to 30.7%, LDL-cholesterol<2.6 mmol/L (100 mg/dL) from 25.8% to 38.1%. Amongst patients with diabetes for 15 or more years, the crude incidence of acute myocardial infarction decreased from 8.7 to 5.8, stroke from 13.5 to 10.1, ESKD from 25.8 to 22.5 and death from 29.0 to 26.6 per 1000-person-years between 2000–2002 and 2010–2013, respectively. 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.[266] In the latest analysis of over 770,000 adults with T2D observed between 2001 and 2016, death from all causes, CVD and cancer amongst individuals with diabetes declined by 52.3%, 72.2% and 65.1% in men, and by 53.5%, 78.5% and 59.6% in women albeit the decline was less evident in young adults between 20–44 years.[57]

There are considerable between- and within-country variations in the care cascade from awareness, diagnosis, treatment to control in both LMICs and HICs.[281] However, on average, the 2–3 fold higher and rising incidence of CVD and death rates in LMICs (e.g., India) as compared with the declining rate of CVD in North America may reflect differences in resources, capacity, access and care organisation. The close association between reduction in risk factors and clinical outcomes in both RCTs and real-world settings provides a strong business case for investing in preventive care by controlling multiple risk factors and empowering patients. This can yield high return after 10–15 years by reducing long-term complications, i.e. 'pay now, save later' rather than 'save now, pay later'.[282] In 2010, the USA spent purchasing-adjusted USD 7,383 per capita for treating diabetes, mainly for comorbidities, compared with less than USD 100 per capita in 16 low-income countries. While the USA spent 52.7% of the global expenditure on diabetes, India spent less than 1% of the world's total, despite having one of the largest populations of diabetes. Counted as a whole, all 18 countries included in the African Region defined by the IDF spent only 0.3% of the global diabetes expenditure.[160]

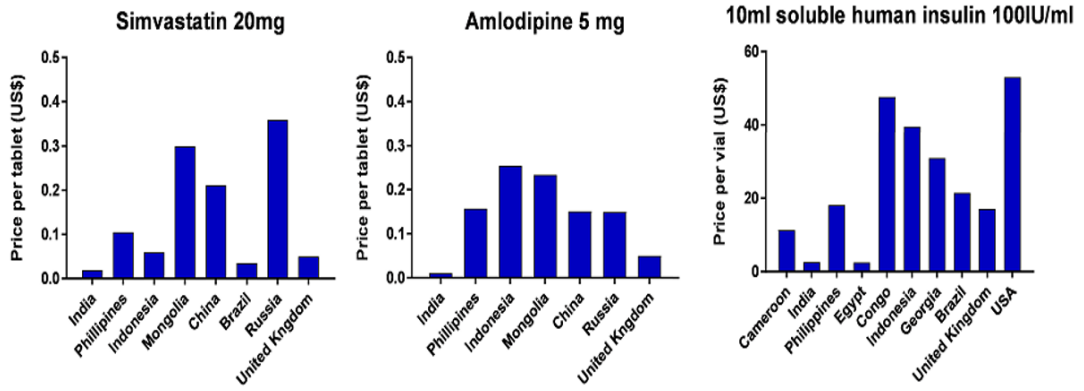
### *7.7 Importance of context-relevant data to guide local practice and policies*

Distribution of resources is often a political decision rather than based on evidence. In LMICs where local data are frequently lacking, funding bodies often have to find the right balance between investing in preventive care for future gains or providing care to patients with more immediate needs. Use of medications is core to diabetes management. Currently, most of the economic evaluations in diabetes focus on blood glucose lowering drugs and devices (e.g., insulin-based treatment regimens),[283] as well as interventions aimed at improving other aspects of risk factor control.[284] A growing number of countries allocate public funds to interventions based on cost-effectiveness,[285,286] which depends on incremental cost and health benefits often expressed as quality-adjusted life-years (QALYs). These analyses often influence reimbursement decisions for pharmaceuticals[287] and, to a lesser degree, medical devices[288] and systems of payment of HCPs.[289] Beyond treatment, there are also economic evaluations of preventive interventions targeting high-risk and specific populations,[290] as well as broader community interventions.[291]

### *7.8 Escalating costs of medications and lifelong care suggest a need to improve the efficiency in care delivery*

In the absence of country-specific and cost-effectiveness data from LMICs, economic evaluations derived from HICs[284] and international RCTs are sometimes used to guide clinical decision at a national level.[292] These analyses suggested blood glucose control using metformin, SU and insulin is cost-effective and is recommended by the WHO.[248,293] Large RCTs also confirmed that control of BP[294] and LDL-cholesterol[295] are cost-effective and (in some cases) cost-saving. With the expiry of patents, the cost of many widely-used therapies (e.g., earlier blood glucose lowering drugs, statins and angiotensin-converting enzyme inhibitors [ACEi]) has fallen markedly in recent years, making these therapies more cost-effective and affordable on a global basis. In many countries, generic drugs for treating individuals with diabetes can be purchased for just a few cents a day. Yet, surveys of drug prices have indicated wide variations across and within countries (Figure 8). These price differences, such as for insulin, are often related to the supply chain structure, mark-up by distributors, wholesalers and retailers and sometimes import duties.[296]

**Figure 8: Price differences in common medications used in patients with diabetes in countries ranked based on gross domestic product per capita in 2011. Prices of simvastatin and amlodipine are pubic sector procurement prices from various surveys conducted by WHO/Health Action International Project on Medicine Prices and Availability between 2002 and 2013. United Kingdom drug prices are based on Category M price. Insulin data are private prices based on a global snapshot on 11 May 2010 as reported by WHO/Health Action International Project on Medicine and Availability.**




World Health Organization. WHO/Health Action International Project on Medicine Prices and Availability http://www.who.int/medicines/areas/access/Medicine_Prices_and_Availability/en/WHO/Health (Accessed o 1 Jan 2018).

In areas where large variations exist in the costs between different types of therapies (e.g., classes of blood glucose lowering drugs), there is a need to assess whether the more expensive therapies provide additional benefits that justify the higher cost. In some countries, national health services and country-wide coverage schemes have enabled more effective negotiations to ensure equitable returns for

manufacturers while retaining security of supply to the consumer. Indeed, the most cost-effective strategies to control diabetes and reduce complications may change over time due purely to changes in the relative cost of therapies, which may influence future practice guidelines.

Although new technologies, including insulin analogues and insulin pumps, have the potential to improve and extend lives of people with T1D, most come at a higher cost than the interventions they replace. Globally, there is great variation in the cost of human insulin especially in LMICs.[297,298] For example, data collected by Health Action International indicates that the price a patient would have paid for a 10 mL vial of soluble human insulin ranged from USD 1.55 to USD 76.69 across different countries.[299] In a recent survey involving 13 LMICs, up to 80% of countries have access to human insulin compared with 60% for insulin analogues, with 3-fold higher price for the latter, more so in the private market. The researchers estimated that a low-income person had to work 4 and 7 days to buy 10 mL human and analogue insulin, respectively.[177] In other countries, 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 amongst manufacturers, reducing unnecessary administrative costs, promoting the use of quality-assured generic medications including biosimilars, or providing subsidy for medications with a ceiling of out-of-pocket payment through public-private partnership may make preventive care more accessible and affordable, as well as reduce the financial impact on patients and their families.[182]

While there are several strategies to promote insulin access in LMICs,[300] lessons can be learned from global efforts to tackle infectious diseases such as human immunodeficiency virus (HIV) infections, malaria and tuberculosis. In these disease areas, global funds have been established by donors to finance innovative research.[301] In the field of diabetes, patients need access to affordable ways to monitor blood glucose.[179] A prize to reward such innovations may replace traditional patent system to increase their affordability.[302] That said, these propositions can have challenging economic and moral issues including striking 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 as well as fund management.[301]

### *7.9 Close the gaps in medical coverage, care organisation and continuity*

Insufficient patient engagement and care fragmentation often lead to suboptimal control of risk factors resulting in complications which substantially increase healthcare costs.[303,304] Healthcare provision and financing are complex issues which need to be context-relevant. An analysis of the 2002−2003 World Health Survey data indicated that patients with diabetes spent considerably more than others on out-of-pocket medical expenses and had a greater chance of incurring catastrophic medical expenses.[305] Generally speaking, without adequate insurance coverage or national provision of good outpatient care which include consultations, medications and investigations, many patients are not willing to pay out-of-pocket for preventive care, often due to lack of urgency or vague symptoms, and thus, miss the opportunities of early intervention.[306] In LMICs, patients with diabetes face a much larger out-of-pocket cost than their counterparts in HICs.[307] In low-income countries, out-of-pocket cost accounted for 43% to 100% of the healthcare spending. In the USA, over 90% of patients with diabetes had healthcare insurance and their out-of-pocket payment accounted for 0–13% of the total health expenditure (Table 1). However, for some high-deductible insurance schemes or medical saving schemes, the need to co-pay may represent a barrier to seeking preventive care especially in low-income populations.[308]

In many patients with diabetes, inability to obtain adequate insurance coverage means that even patients with reasonable means may suffer huge financial loss once these complications develop.[309] A recent decision by the state of Oregon in the USA to expand its Medicaid Programme gave researchers the opportunity to evaluate the impacts of expanding insurance coverage. The results indicated that those who received insurance had a greater probability of receiving a diagnosis of diabetes and using medications for diabetes.[310] Similarly, among adults with diabetes in the USA, acquiring Medicare insurance coverage was associated with a greater increase in physician visits.[311] There is also evidence from outside the USA that insurance positively impacts on healthcare use. In Mexico, the introduction

of public health insurance (*Seguro Popular*) has led to an increase in the use of insulin and oral medications in patients with diabetes,[312] although the impact of insurance on disease control for patients with diabetes is mixed.[310]

In Japan with universal health coverage, there remain considerable variations in quality indicators including assessment for complications and risk factors, attainment of treatment targets and use of life-saving medications with better performance amongst institutions with certification.[313] In some HICs, as many as 50% of patients defaulted follow-up visits, especially amongst young and/or newly-diagnosed patients. These defaulters were more likely to have poor control of risk factors, develop complications, attend emergency departments or require hospital admissions compared with patients receiving continuing care.[314-316] In a survey including patients with T2D from HICs (Australia, France) and LMICs (Latin America), despite the marked differences in national healthcare investment, the proportion of patients receiving recommended care processes and achieving recommended treatment targets remained remarkably similar. These data suggested that healthcare investments aside, care organisation aimed at improving access and reducing default are important determinants for outcomes.[317] Here, professional training, patient education and registers are additional strategies needed to add value to care delivery with exemplary examples in both HICs and LMICs.[318]

Mandates, incentives and audits are universal pillars in healthcare reform, applicable to most healthcare systems.[319] These strategies can be used to guide payers and users to distinguish between high- and low-value services, supplemented by payment schemes to encourage the provision and subscription of value-added services.[320] In areas where both private and public sectors provide healthcare, alignment amongst payers, patients, providers and industry may allow more efficient use of emergency, inpatient and outpatient care in both sectors.[321] In Argentina, medication costs in patients with T2D were driven by long disease duration and complex therapies although good glycaemic control reduced overall cost.[322] In a multistaged quality improvement programme aimed at enhancing professional knowledge, patient self-management and access to medications in primary care setting, supplemented by registers for quality assurance, there was improvement in clinical outcomes with cost-saving.[323] In the UK, introduction of the Quality and Outcomes Framework (QOF) in primary care with financial incentives has led to improvements in both process and outcome measures.[324] In Asia, several governments including China, Taiwan, Hong Kong, Singapore have adopted a data-driven strategy by providing or subsidising structured risk assessment, education and management programmes.[325,326]

## 8 Interventions directed at population-wide and at high-risk individuals for prevention of T2D

Given the lifecourse and multidimensional nature of diabetes including environment and lifestyle factors, a multipronged, multitiered and multisectoral strategy is essential to prevent and manage diabetes. This could include, but is not limited to, the use of fiscal measures to protect the environment with better city planning, control of emission of air/water pollutants, regulation of food safety and quality, introduction of sugar-tax, designation of tobacco-free public areas and creation of healthy cities with more 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 education through provision of secondary school education and increasing health education in early school curriculum, may improve health literacy and help raise disease awareness. Finally, better maternal and child health will play important roles in the lifecourse prevention of diabetes, although more research is needed to identify high-risk mothers and children for more targeted interventions.[327]

The societal measures aimed at improving the wider determinants of health-related behaviours are in accordance with the United Nations Sustainable Developmental Goals, where quality education, environmental and social protection along with an appropriately functioning healthcare system are key to a sustainable economy. Practitioners, researchers and managers, who have expert knowledge in the multidimensional nature of diabetes as well as 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 policymakers, corporations and civic community. These concerted actions are needed for designing,

implementing and evaluating a context-relevant and integrated society-community-individual strategy aimed at changing the ecosystem, improving the healthcare environment and ensuring healthcare equity for preventing and controlling obesity, diabetes and other NCDs.[328]

### *8.1 Preventing T2D can prevent CVD – challenges and opportunities*

Several RCTs and meta-analyses have confirmed that T2D can be prevented by lifestyle interventions in closely-supervised situations.[329-333] In China, lifestyle intervention in middle-aged men with IGT reduced conversion to T2D by 40% at 6 years. After the study was completed, the intervention group continued to benefit with 20% risk reduction for retinopathy, CVD and all-cause death 30 years after the trial commenced.[256] The benefits of lifestyle interventions with or without medications including metformin, alpha-glucosidase inhibitors and thiazolidinediones in reducing onset of T2D in individuals with IGT and multiple cardiometabolic risk factors have also been reported in studies conducted in the USA, Europe, India and Japan. Similarly, lifestyle interventions also reduced hypertension in individuals without IGT.[334,335] This evidence has led to the establishment of systematic, high-risk individual-level T2D prevention programmes in HICs such as Germany, Finland, the USA, the UK, Poland and Singapore. Real-world implementation of these lifestyle intervention programmes with less intensity has yielded favourable results in countries from Asia, Africa and the Middle East (Table 3).

Translating evidence to practice should consider both the absolute risk of future T2D in that individual, as well as the risk reduction that can be achieved by the intervention. These parameters form the basis of the absolute risk reduction (ARR, difference between the event rates in the control and experimental group), and the number needed to treat (NNT, inverse of ARR). Thus, for the same risk reduction, high-risk individuals will gain more from the intervention with lower NNT to achieve positive outcomes. Countries that have translated this evidence often adopt an integrated approach of establishing guidelines, training an effective workforce of non-physician lifestyle coaches along with various types of HCPs, monitoring quality through simple registers, encouraging reimbursement, raising awareness and marketing the programmes.[336,337] To date, the evaluation of the National Diabetes Prevention Programme in the USA has demonstrated rapid increase in trained lifestyle coaches and participation, as well as favourable weight loss of 4% at one year that is generally in line with the magnitude of weight loss observed in community translation trials.[336,337] This programme has also achieved healthcare 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.[338]

Compared with research settings often confounded by volunteer bias and close supervision, the uptake of the screening and intervention programmes and intensity of intervention in real-world practice is often not as high.[339] In the USA, the MOVE–IT (MOtiVational interviewing InTervention) trial 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 CVD identified during routine health checks.[340] 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 fraction of the population for whom the intervention was designed. Other barriers in implementing primary prevention programme include economic constraints, insufficient resources, cultural taboos, poor health-seeking behaviour and lack of knowledge and skills.[341] To this end, some researchers used behavioural economics such as giving financial incentives to increase physical activity, using visual cues to encourage selection of heathy food choices or losing deposits for not reaching targets in a contract of weight reduction.[342] These studies have yielded encouraging results, suggesting similar approaches can be further explored.

A critical 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. Common methods that have been employed include word of mouth, information through flyers and posters, advertisement, recruitment through existing programmes, conducting community screening programmes, recruiting selective populations (e.g., using risk scores), as well as targeting family members of patients with diabetes and staff of corporations. There are few studies that examine the most effective approaches to identify high-risk individuals relevant to the local population and healthcare setting. It is also unknown

whether approaches that work in developed countries, with generally high literacy and well-supported primary care system, are translatable to other settings where illiteracy and availability or access to primary care are important barriers. These challenges have fuelled a new wave of research into the science of engagement and uptake, as well as tailored modalities of delivery to optimise participation and effectiveness. In a recent meta-analysis of real-world T2D prevention programmes, group intervention using community health workers or professionals were similarly effective with weight loss as the major determinant, the latter being closely associated with levels of engagement.[343] Thus, by developing and evaluating innovative multicomponent care models, including but not limited to, technology and trained community health workers/peers with linkage to healthcare system, these challenges are not insurmountable.

### *8.2 Use of technology and non-physician personnel may enhance the cost-effectiveness of lifestyle interventions*

In a systematic analysis of 28 studies, the economics of lifestyle intervention programmes conducted mainly in HICs, consisting of at least 2 sessions in 3 months delivered to people at increased risk of developing diabetes was analysed using cost expressed in USD in 2013. The median programme cost per participant was USD 653 with lower costs for group- (USD 417) and community/primary care-based programmes (USD 424). This is compared with USD 5,881 for the DPP (Diabetes Prevention Program) trial and the DPP Outcomes Study (DPPOS). From a health system perspective, the median incremental cost-effectiveness ratios (ICER) was USD 13,761 per QALY saved. Group-based programmes were more cost-effective (USD 1,819 per QALY) than individual-based programmes (USD 15,846 per QALY).[344] More recently, in a 15-year analysis of the DPP/DPPOS which also included a metformin intervention arm, metformin was found to be cost-saving in preventing diabetes with reduced long-term complications, especially amongst those with obesity, high fasting plasma glucose or a history of gestational diabetes.[345]

As a general rule, interventions are more cost-effective when the intervention is targeted at individuals who are at a high absolute risk of T2D,[346] and when the interventions are delivered in a group format by trained community health workers/peers. The advent of mobile health (mHealth) programmes offers an opportunity for developing potentially scalable and cost-effective prevention management strategies for diabetes and other NCDs especially in LMICs.[347] In India, a short message service (SMS) study using mobile phones to provide health behaviour messages to men with IGT found a 36% relative risk reduction in the development of T2D after two years.[348] 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 T2D. It is expected that the trained personnel will disseminate knowledge to the local community by organising awareness programmes. Similarly, promising internet- and social media-based approaches to supporting lifestyle changes are underway, but data on the long-term outcomes of these programmes from RCTs are not available.[349]

In a multicentre study conducted in South America, a 12-month mobile phone-based health intervention using monthly motivational counselling calls and weekly personalised text messages resulted in meaningful reduction in BP and body weight which was sustained after 6 years, especially amongst those who received at least 50% of the calls.[350,351] Indeed, the use of information and communication technology (ICT) such as wearable devices to monitor physical activity, sleep pattern, pulse rate, BP and blood glucose, along with mobile applications (APP) 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, encourage behavioural changes such as improving healthy dietary habits, encouraging physical activity and losing weight.[352]

Although these results support the potential of using digital health solutions to increase the reach and impact of lifestyle intervention and weight management programmes, healthcare workers and professionals are often needed to improve engagement, suggesting that a 'high tech, soft touch' approach may address the psychosocial and informational needs of these individuals.[343] Similar to drug

development, there are investment costs for developing, marketing and maintaining these technologies with return of investment as a key consideration. Thus, until there are high levels of evidence, supported by cost-effectiveness analysis, sustainable engagement and willingness-to-pay are major challenges in the scaling up of these prevention programmes.

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

In RCT setting, individual-level lifestyle intervention aimed at changing obesity, diet and physical activity has generally had a similar impact in all populations and in all ethnic subgroups within populations.[353] However, these observations may be obscured by the dominance of participants from HICs. Compared with Caucasians, Asians have lower acute insulin response for the same decrement in insulin sensitivity.[109,354] In these populations, a small increase in adiposity, especially if central, can worsen insulin resistance and decompensate beta-cell function. While weight reduction in these high-risk individuals may reduce risk of diabetes, alternative strategies targeted at ameliorating glucotoxicity to preserve beta-cell function, especially in lean individuals with glucose intolerance needs further exploration.[89] Approximately half of all individuals in T2D prevention RCTs are from Europe and the USA. The other half are from India, China and Japan. Without representative data from other regions, it is difficult to extend the cost-effectiveness of T2D prevention interventions from HICs to LMICs where data are scarce.[290] Besides, given the lack of information of other population-based risk factors and population attributable risk due to societal determinants, notably poverty and education,[151] maternal nutrition, early-life stunting,[355] infections of various kinds,[356] dietary factors and environmental factors such as pollutants which are highly prevalent in LMICs (Table 2),[357] the cost-effectiveness of these lifestyle intervention programmes remain uncertain.

### *8.4 From effectiveness to efficiency of T2D detection and prevention programmes*

Nearly all T2D prevention trials have focused on interventions in individuals with IGT. However, in real-world practice, the 75-gram OGTT is rarely used to detect abnormal glucose tolerance (i.e., impaired fasting glucose [IFG] and/or IGT) and few individuals have measurement of 2-hour post-challenge glucose levels, needed to diagnose IGT. Although there is epidemiological evidence suggesting that $HbA_{1c}$ predicts incident diabetes and CVD in a non-diabetic population in a linear manner,[358,359] there is very limited evidence regarding the benefits of T2D prevention programmes among those with isolated IFG or with isolated, elevated $HbA_{1c}$.[360] There are also knowledge gaps regarding the effects of haemoglobin variants[361] and thresholds for haemoglobin glycation which can influence the diagnostic values of $HbA_{1c}$ in different ethnic groups.[362,363]

Additionally, hyperglycaemia *per se*, regardless of the definition used, may not be the best way to target high-risk individuals while its combination with other information into a risk score is more robust in predicting risk for diabetes.[364] These risk factors can be based on questionnaire (e.g., family history of diabetes, use of tobacco, history of maternal hyperglycaemia, hypertension, high blood cholesterol, non-alcoholic fatty liver disease (NAFLD) and/or polycystic ovary syndrome) and self-measurement (BP, BMI, waist circumference) for incorporation into various risk scores to detect high-risk individuals for intervention. There are now many published risk scores which require validation and calibration when applied to a different population.[365] These unanswered questions aimed at identifying individuals who will benefit most from lifestyle intervention requires further research and evaluation in order to assist decision-makers in delivering the intervention in the most efficient and cost-effective manner.

Pharmacotherapy, such as low cost metformin, may have a place either as an alternative or as an adjunct intervention.[345] However, pharmacological T2D prevention implies that an individual will receive a diagnosis and glucose lowering therapy and attend a physician regularly for monitoring. Given the large number of people at risk, intervention using medications such as metformin which is at best effective only in 10-15% of people with IGT, and medical procedures, should not be considered without a high level of certainty. That said, given the effectiveness of lifestyle intervention and metformin, in individuals at high risk of conversion or in those with practical difficulties in adhering to structured

lifestyle intervention, a combination of metformin and lifestyle intervention, or early-stage metformin as an alternative to lifestyle intervention are options worth exploring.

One of the limitations in these trials is the proxy endpoints since the goal of T2D prevention is not solely to reduce the incidence of T2D, but also to reduce its clinical complications.[366,367] Since CVD is the leading cause of death in diabetes or abnormal glucose regulation, there is also strong argument of using a polypill-based strategy. The latter contains a fixed-dose of several inexpensive medications such as metformin, statins and RASi, which may prevent both T2D and CVD and should be a key priority for governments and/or other sponsors including pharmaceutical industry.[368] Several RCTs have demonstrated the effectiveness of using polypills to improve the control of multiple risk factors including BP and lipids in both HICs and LMICs.[369-371] In a 5-year RCT conducted in Iran involving middle-aged individuals with CVD and/or cardiometabolic risk factors, treatment with a four-in-one-pill (hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg and enalapril 5 mg) reduced CVD by 20-40%, depending on prior history of CVD, with overall good safety and adherence.[372]

### *8.5 Short- and long-term impact of primary prevention of T2D on healthcare utilisation*

The decision to introduce systematic screening for undiagnosed diabetes in many settings has been guided by the WHO criteria for screening programmes.[373-375] 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 about three years. Based on data from the ADDITION-Europe cohort, researchers simulated models which indicated that screening followed by multifactorial management resulted in 3.3% ARR and 29% relative risk reduction (RRR) at 3-year and 4.9% ARR and 38% RRR at 6-year for CVD.[376] Although long-term observational data from the ADDITION cohort has yet to confirm the benefits of screening on CVD or all-cause mortality,[377] recent health economic analysis from Denmark suggests lower healthcare costs in the screened-group compared with the non-screened group, with the screening programme being cost-saving amongst those who were screened positive.[378] A mathematical modelling exercise has suggested that in the US population, screening for T2D would be cost-effective when started between the ages of 30 years and 45 years with screening repeated every 3-5 years.[379]

Most experts recommend a screening strategy targeted at high-risk individuals with aforementioned risk factors and risk markers such as obesity and high BP which can be self-assessed. These data can be used to compute risk scores to detect high-risk individuals followed by confirmatory laboratory tests including 75-gram OGTT and/or $HbA_{1c}$.[365] Pending evidence regarding the best screening strategy, systematic reviews including economic analysis suggest that promoting healthy diet and physical activity especially if delivered in groups or in primary care setting, targeting high-risk individuals can be cost-effective in both HICs and LMICs.[343,344,380]

In LMICs with the least affordability to pay for expensive, late-stage complications, there appear to be strong economic argument to screen for high-risk individuals for lifestyle intervention. However, this strategy will undoubtedly lead to identification of a large number of individuals with previously undiagnosed diabetes, which can be as high as 70% in some LMICs.[381] In a nationwide screening programme conducted in Brazil, individuals aged 40 years or above were invited to undergo capillary blood glucose testing at primary healthcare centres through mass media and awareness campaign. Individuals with positive test were recalled to undergo confirmatory test using fasting plasma glucose. The programme aimed at detecting undiagnosed diabetes and building capacity of primary care teams. Amongst 22,069,905 screening tests performed, 3,417,106 (15.5%) were screened positive. Amongst them, 10% (n=346,168) were confirmed as new cases with 92.2% (n=319,157) being incorporated into the healthcare system.[382]

The uncovering of this large population of individuals with undiagnosed diabetes who need continuing care, assessment, education and medications have huge resource implications, which may compromise the care received by those diagnosed through standard clinical channels, as well as compete for the resources needed for primary prevention using lifestyle intervention. Even for programmes aimed at

detecting and treating HIV infections, supported by philanthropic funds, there are still persistent gaps in achieving targets.[383]Thus, the implementation of large-scale and resource-efficient T2D prevention programmes, targeting high-risk individuals and detecting/treating undiagnosed diabetes should be supported by a prepared healthcare system.[384,385] In LMICs, this will necessitate upfront investments in building infrastructures and capacity.[386] To maximise the use of finite resources, inter-sectoral collaborations and public-private partnership are needed to develop an integrated system using physicians and non-physician personnel to cover 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 T2D epidemic, tailored according to each country's particular environmental and political contexts.

### *8.6 Population and individual-level prevention – getting the right balance and how to evaluate*

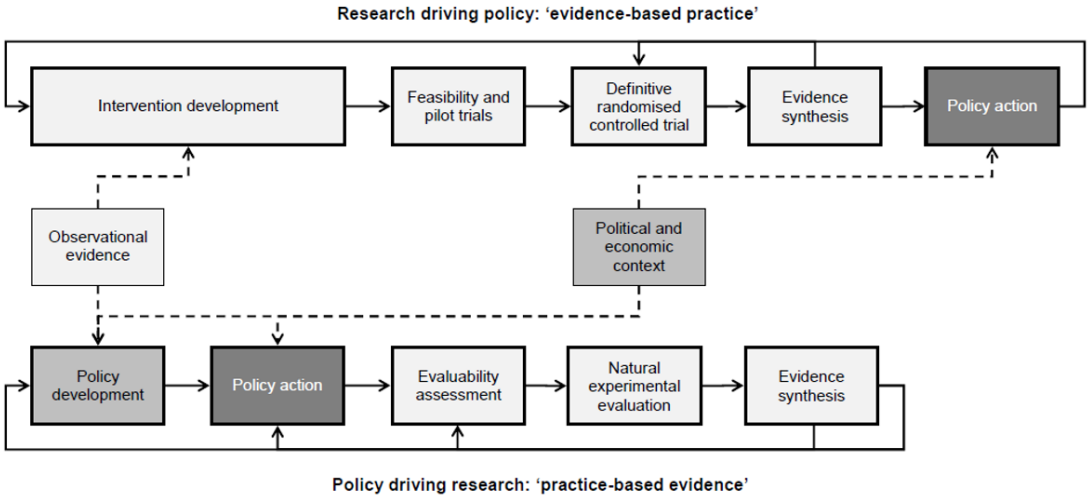
The risk factors that are the targets of effective individual-level interventions (e.g., lifestyle intervention) should also be targets for population-level interventions,[387] although adoption of a population approach calls for better understanding of the key determinants of the environmental and behavioural drivers of T2D risk, relevant to the area concerned. Physical activity, dietary behaviour and obesity levels are often seen as an individual's decisions or preference. However, these behaviours and social norms are driven principally by more upstream societal-level factors such as the overall food supply, price, marketing, the sedentary nature of most modern occupations, the lack of availability of health-promoting transport options and the structure of the built environment. Seen from this perspective, the emergence of T2D is predominantly a societal problem for which societal-level solutions are also required.[388]

Table 2 summarises a range of social, developmental, environmental and behavioural risk factors for which the evidence of association and population attributable risk is less clear. The extent to which these risk factors could be modifiable and could 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 where interventions are developed, usually using RCT design, and tested in multiple populations and settings. Once the intervention is found effective, this is followed by meta-analyses and systematic reviews of similar results which will contribute to the formulation of evidence-informed practice guidelines and public policies, as in the case for diabetes management and T2D prevention in high-risk individuals.[389]

There are a few examples of population-level interventions where researchers used RCTs to demonstrate the effects of using salt substitution to reduce blood pressure[390] and that of using housing vouchers and counselling to encourage women and their children to move out from a high poverty to a low poverty areas with reduced prevalence of extreme obesity and diabetes.[391] Although this reductionist RCT approach follows the classical teaching, given the threat posed by T2D, bold policy-level action followed by evaluation using a range of quasi-experimental methods is an alternative approach (Figure 9).[392] In this fundamentally different approach, the best available observational evidence is used to support a policy-level intervention which is then evaluated in the real-world using quasi-experimental methods. Measures to cut tobacco use[393] to reduce deaths, and mandatory seat belt use to reduce road traffic injury have followed this approach.[394]

In Scotland, a policy intervention which 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 impact on ischaemic heart disease. Compared with the number of admissions due to acute coronary syndrome in the 10-month period prior to the passing of the legislation, there was a 17% reduction during the same period in the following year after its enactment.[395] When similar interventions have been implemented elsewhere, evidence synthesis of the effectiveness of tobacco control strategy was then possible using meta-analysis.[396] Given the multidimensional nature of diabetes, multiple societal-level interventions will be required, albeit each of which may only have a small effect. For example, policies to implement sugar-sweetened beverage taxes and levies are increasingly being evaluated[397] but such evaluations are usually focused on proximal outcomes like purchasing or consumption. In this type of policy intervention, more distant outcomes such as incidence of T2D, have to be modelled rather than directly observed.[398]

**Figure 9. Routes to the translation of evidence into action in clinical and public health interventions (Ogilvie D et al SocArXiv 2019).**




### *8.7 Primary prevention of T2D requires bold evidence-informed political actions*

In recognition of the lifecourse nature of diabetes and other NCDs, members of the Commission reiterate the importance of using educational policy at all levels, including 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. We also emphasise the importance of using environmental policies to build healthy cities through inter-sectoral 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 T2D, we also re-affirm the importance of tobacco control as an important policy in the prevention of T2D and its complications. These societal strategies are accord with the 'best buys' from the WHO[327,393] and the recommendations by the United Nations Sustainable Developmental Goals.[399]

Within this framework, members of the Commission further proposed a series of possible actions which could be undertaken by governments and policymakers at the supranational, national, regional and local levels to influence those risk factors (Table 3). The approach used in any given setting will be determined not only by epidemiological considerations of expected benefit but by considerations of political feasibility. The cost-effectiveness of some of these population-level interventions have been evaluated, including sugar-sweetened beverage taxes,[400] restrictions on unhealthy food advertising,[401] mass media campaigns to promote healthy lifestyle[402] and economic incentives to increase fruit and vegetable consumption.[403,404]

Since the effectiveness of such interventions cannot be determined from RCTs, simulation modelling is often used to estimate their cost-effectiveness. The evidence from the few studies available suggests that these interventions are generally cost-saving or cost-effective.[405] 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. As they are relatively inexpensive, these interventions 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. As estimates of both cost and effectiveness of population-wide interventions have been modelled-up from numerous assumptions, rigorous natural experiments are needed to evaluate effectiveness and help prioritisation and implementation of such approaches.

Decisions to allocate resources for screening, prevention and treatment are often context-relevant taking into consideration local cultures, socioeconomic development and existing capacity of healthcare

systems. That said, given the life-threatening nature of untreated or poorly-managed diabetes, it is important that all healthcare settings act promptly to provide care meeting minimal standards to all individuals diagnosed with diabetes. Amongst those who are in contact with the healthcare setting and have a high likelihood of having prevalent but undiagnosed diabetes, they should have a diagnostic test, and if positive, be included into the same system of care as those people with known diabetes. The implementation of more systematic approaches to find individuals with undiagnosed diabetes and those at high-risk of future diabetes is a contextual healthcare policy decision, influenced by the structure of individual healthcare systems.

### *8.8 An example to illustrate priority actions in HICs versus LMICs*

Depending on the environmental, political and social context, the policymakers will need to adopt a multicomponent strategy to combine population-wide and individual-level interventions aimed at high-risk individuals. Most literature suggests that obesity, physical inactivity and different dietary and nutritional factors are amongst the most modifiable risk factors, which form the basis for many of the individual-level primary prevention programmes. Using the USA as an example, the population attributable risk due to obesity, poor diet and physical inactivity was 87% amongst women, suggesting that the overwhelming majority of cases of T2D could be averted if women could adopt a healthy diet, by being physically active and not obese.[406] However, the dominance of Western populations in the literature on risk factors and T2D risk (Table 2) and the lack of data from Asian and African populations raise the question whether estimates of population attributable risk could well differ between populations. It is here that local data regarding the population attributable risk due to risk factors such as access to healthy food choices, food insecurity, nutrition, sleep pattern, physical activity and psychosocial stress taking into consideration demographic, environmental and socioeconomic determinants become important for prioritising actions.

The balance between high-risk individual-level prevention and societal approaches to prevention may differ between countries and may also differ within a country over time. Countries should take into consideration the scale of the diabetes problem in their own populations and the ratio of diagnosed to undiagnosed cases, the capacity of primary healthcare systems to undertake screening for undiagnosed diabetes and hyperglycaemia, the capacity for the system to care adequately for additional cases and to provide systematic preventive interventions to those at risk.

As an example, Table 5 compares characteristics of England and Jamaica. 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. There is a strong and well-funded primary healthcare system with the majority of individuals 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 T2D screening and lifestyle intervention programme which will complement population-wide prevention strategies.

In Jamaica, by contrast, funding is far lower and many individuals with diabetes do not even have access to complication screening or risk factor control. In this resource-poor context, a change in the healthcare system to improve diabetes care for the existing population is a priority.[407] Although it might seem intuitive to encourage investment in screening for high-risk individuals for individual-level intervention, this would risk destabilising an already stretched healthcare system. Given the scale of the problem, in addition to improving care standards and health knowledge using non-physician personnel and ensuring access to essential medications, it may be preferable to give even greater priority to interventions aimed at shifting risk factors in the whole population. Caribbean countries have, for example, taxed sugar and are implementing other fiscal measures. This contrast between England and Jamaica illustrates the need for countries to consider a range of epidemiological, economic and healthcare system factors in determining the appropriate balance in any individual country between investments in improving the healthcare of individuals who have diabetes now, interventions in those who will get it soon and more upstream changes that have the potential to influence risk in future generations.

### *8.9 A global epidemic requires local solutions through collective efforts*

We are living in a rapidly changing world where globalisation and technological advancement have increased life expectancy in many parts of the world. These forces have created big changes in 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 subject to external and peer influence, these societal changes have transformed our perspectives, expectations and behaviours leading to new social norms, notably our lifestyles associated with city-dwelling. Rapid rural-urban migration has led to progressive widening of social disparities and increasing income inequality, in part 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 is a wake-up call to the global community on how patients with diabetes and NCDs, especially those with poor access to care and social deprivation, were disproportionately affected during these emergencies. The large number of people affected overwhelmed the healthcare system, even in HICs, with enormous human suffering and economic repercussions.[408-411] In this light, most healthcare systems in LMICs are traditionally designed to treat acute injuries and communicable disease. Not only are these low-resource systems unable to cope with these global emergencies, they are also ill-prepared to manage this growing number of individuals with diabetes and their long-term complications. The rudimentary primary care systems and insufficient experience, skills and exposures for most HCPs against a backdrop of rapid knowledge and technological advancement in the field of diabetes and other NCDs, mean many individuals are not diagnosed, treated or controlled in a timely manner.

Even in affluent areas, decades of social and medical care consumed by this growing population is having an enormous toll on their well-resourced healthcare systems. Many decision-makers have little information to plan resource allocation in order to design, develop and sustain a high-quality integrated diabetes prevention and care service for long-term benefits. The sheer number of individuals with or at risk of diabetes also deter many payers including insurers, governments and corporates to invest and opt for status quo,[412] despite the cost-effective or cost-saving nature of these T2D prevention and care programmes.[413] Improving care aside, strong political will and inter-sectoral collaborations are needed to tackle many of these societal determinants, notably environment, education and poverty, closely linked with diabetes.

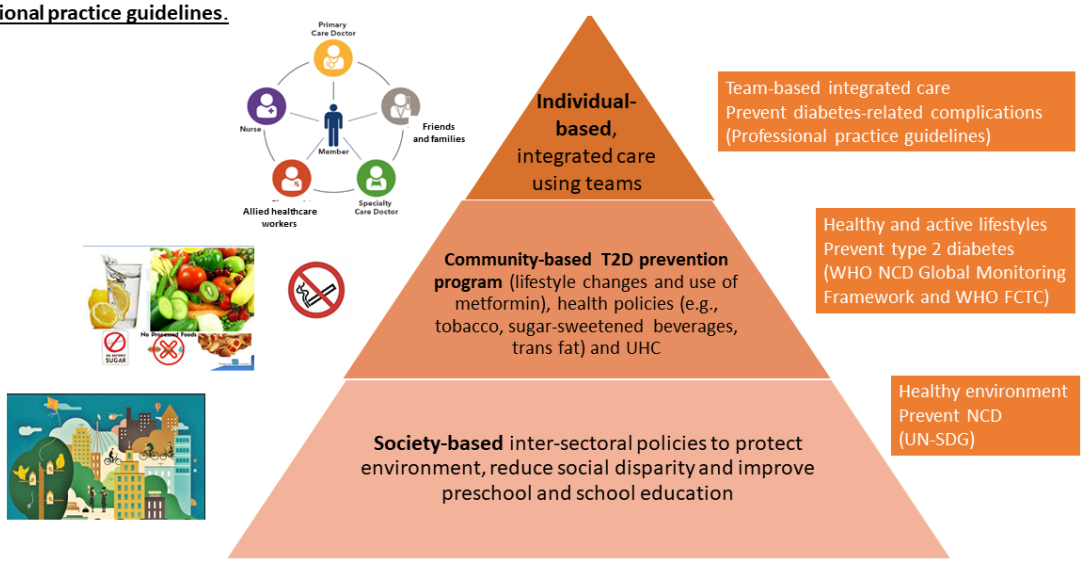
### *8.10 An integrated society-community-individual strategy to reduce burden of diabetes and other NCDs*

Given the multidimensional nature of diabetes, it follows that a multidimensional solution is needed to create short-, mid- 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. Once diabetes develops, care fragmentation and insufficient patient engagement can worsen control of multiple risk factors leading to multiple morbidities. Due to the silent nature of diabetes, phenotypic heterogeneity and pluralistic needs, we argue strongly for the need to redesign the practice environment, team structure and workflow in order to gather data systematically, stratify risk, personalise care, provide feedback and perform periodic monitoring. By establishing community-based diabetes teams/centres and building a strong primary healthcare system with linkage to the hospital-based healthcare system, trained diabetes teams will be in a prime position to identify high-risk individuals for lifestyle intervention including the use of metformin and other medications (e.g., polypill) to prevent T2D and CVD.

This individualised approach needs to be complemented by policies that support building smoke-free, healthy cities aimed at reducing environmental pollutions, ensuring food security, increasing affordability of healthy foods, promoting healthy eating (e.g., nutritional labelling, school meals), encouraging physical activity (e.g., walking paths, sports) and avoidance of harmful substances (e.g., tobacco, sugar-sweetened beverages, trans fat) using taxation and warning labels.[414] To reduce the long-term burden of diabetes and other NCDs, we need to use inter-sectoral polices to improve the ecosystem,

protect the environment and reduce social disparities. Apart from promoting universal health coverage, providing education starting from preschool up to at least secondary levels will help improve literacy closely linked to better health awareness and disease prevention (Figure 10).

**Figure 10. A conceptual framework for a multicomponent society-community-individual strategy to integrate primary and secondary prevention supported by health and inter-sectoral policies including universal health coverage (UHC), preschool/school education and social/environment protection in line with the United Nations Sustainable Developmental Goals (UN- SDG), WHO NCD Global Monitoring Framework, WHO Framework Convention for Tobacco Control (FCTC) and professional practice guidelines.**




## 9 Interventions directed at patients with diabetes and the healthcare systems

The inter-ethnic differences in clinical outcomes, such as high rates of diabetic kidney disease reported in non-Caucasians compared with Caucasian population in epidemiological surveys[415] were considerably attenuated in RCT settings where access to care and support is more assured and structured.[216,416] Compared with the younger and newly-diagnosed patients in the UKPDS conducted in the pre-statin and pre-RASi era,[262,263] participants with either CVD or multiple risk factors in landmark studies including the ACCORD,[229] VADT[230] and ADVANCE trials[231] had 50% lower incidence of CVD and death. In the Steno-2 Study[417,418] and J-DOIT3 Study where patients received intensive treatment to control multiple risk factors, there were marked reductions in cardiovascular-renal events and death rates.

As an example, the J-DOIT3 Study recruited 2,280 middle-aged Japanese patients, of whom 11% had prior CVD. Patients randomised to the intensive treatment group were informed of their treatment targets and given equipment to monitor their BP and blood glucose at home with access to nurse education, whilst their attending physicians were asked to reduce their risk factors within 6 months. This multicomponent strategy had led to extremely low events with no ESKD events and less than 100 CVD events at 8 years. These examples demonstrated how the delivery of structured and continuing care using a team approach with regular monitoring and access to life-saving medications such as statins and RASi can lead to dramatic reduction in clinical events and death rates as compared with that observed in usual care settings.[419,420]

### *9.1 Close knowledge gaps in patient-important outcomes to improve psychological health and behaviours*

Although RCTs and meta-analyses[208,210,211] have confirmed the benefits of reducing multiple risk factors in improving clinical outcomes, the volunteer bias of participants and investigators as well as the artificial nature of the trial settings, pose major challenges in translation in part due to poor access, affordability and adherence. Few RCTs reported patient-important outcomes such as quality of life, treatment costs (direct/indirect) and use of hospitalisation resources as primary outcomes.[421] Compared

with the large number of RCTs evaluating technologies, few research studies examined the socio-economical-cultural factors which underlie behavioural changes in order to achieve 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, the lack of consideration of patient's socio-personal context, personal values and preferences have reduced their relevance and effective implementation especially in LMICs or low-resource settings.[422,423] In some vulnerable populations due to social inequalities or cultural barriers, using outreach programmes or community-based centres may improve access to care compared with traditional clinic- or hospital-based settings. Similarly, using trained non-physician personnel (e.g., trained community health workers/peers) to empower and support these individuals (and their families) to manage stress and solve problems during their day-to-day living with diabetes may enhance their resilience in self-management.[424]

In order to translate these efficacy data in trial settings to cost-effectiveness data in real-world practice, we need to develop frameworks where environment, care settings, providers, processes, supporting systems and payers are aligned in order to create impacts.[425] To close these knowledge gaps, investment is required to fund new research methods and studies conducted in real-world setting with publications of these results in leading academic journals in order to create a paradigm shift focusing on implementation and evaluation in real-world setting.[426]

### *9.2 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 United Nations Sustainable Developmental Goals 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 in order to achieve positive outcomes. Using the physician per inhabitant ratio as an index of capacity, the figures in 2018 ranged from 5.0 per 1,000 in Cuba, 3.9 per 1,000 in Argentina to 0.02 per 1,000 in Malawi. In the top three countries with the largest number of individuals with diabetes, the figures were 1.5 per 1,000 in China, 0.6 per 1,000 in India and 2.3 per 1,000 in the USA. In Europe, the figures were 2.85 per 1,000 in the UK, 3.17 per 1,000 in France and 3.99 per 1,000 in Italy. Even in countries/areas with ratios higher than the recommended ratio of 1.9 per 1,000 by the WHO,[427] there is a need to train non-physician personnel to assist physicians to provide continuing care of these individuals with multiple needs.

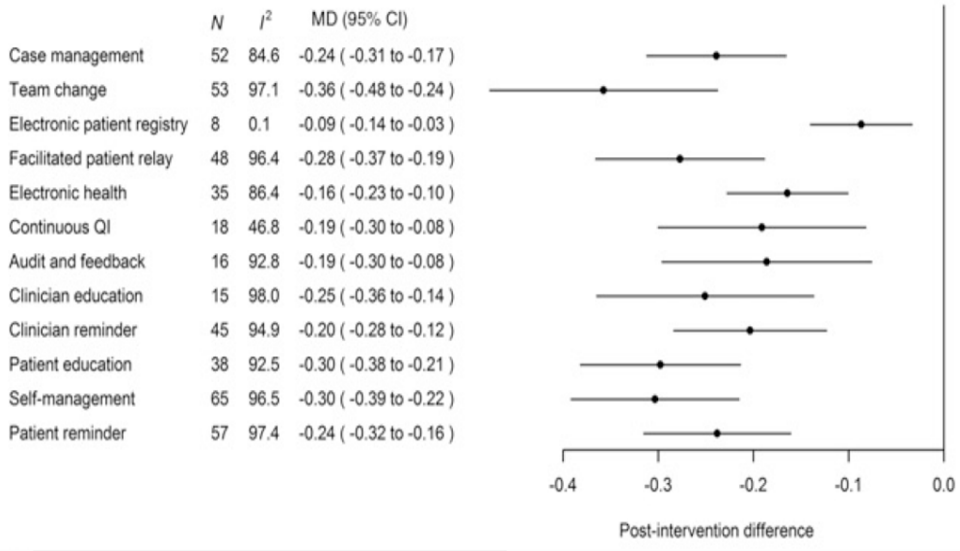
During the life journey of an individual with diabetes, he/she may need professional advice from specialists, family doctors, allied healthcare workers (e.g., nurses, dietitians, social workers, pharmacists). Apart from friends and families, these individuals may need, but frequently do not have continuing support from trained community health workers/peers with well-delineated roles, in order to cope with the day-to-day challenges posed by self-management.[428] In many LMICs, knowledge transfer from skilled workers to community health workers and trained peers may be the only way to meet the huge service demands, pending healthcare reforms and capacity building. In the 'Step by Step Foot Project' piloted and carried out in India and Tanzania, education of both HCPs and patients about proper limb care are used to reduce amputation.[429]

While we emphasise the use of non-physician personnel to make diabetes care more accessible and sustainable, given the large number of patients requiring diabetes care with different levels of complexity and shortage of HCPs with special knowledge in the field, especially in LMICs, policymakers, payers and planners are urged to increase investment and develop diabetes as a specialty in order to improve care standards, provide training and conduct research for informing practices and policies. Apart from building infrastructures, there is an urgent need to advance career paths of HCPs with appropriate knowledge and skills in order to reorganise care, develop teams, provide on-job training and teach undergraduate students in order to close the gaps in professional knowledge as a prerequisite to delivering high-quality diabetes care.[430,431]

### *9.3 Use 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 impacts of quality improvement. By promoting quality improvement as a science, HCPs, planners, managers, payers, researchers and users of the system, i.e., people with the conditions, can collectively design systems, train staff and develop protocols to improve the quality of care with ongoing data collection to identify care gaps and evaluate effectiveness.[432] In Mexico, implementation of a comprehensive programme to define risk profiles, individualise care and empower patients resulted in significant improvement in attainment of $HbA_{1c}$ target and negative emotions, although the proportion of patients who persisted with the programme at 12 and 24 months declined by more than 50% and 75%, respectively.[433] In a meta-analysis of multicomponent quality improvement strategies targeting systems, patients and HCPs for 12 months or more, task shifting, patient education/self-management support and facilitated relay (using nurses, healthcare assistants [HCA], trained community health workers/peers, information technologies) to improve patient-provider communication have the largest effect sizes in reducing $HbA_{1c}$ (Figure 11) with similar improvements for BP and LDL-cholesterol.[275] 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.[323,434,435]

**Figure 11. A meta–analysis of 181 trials showing the effects of different quality improvement strategies targeted at patients, providers and systems on $HbA_{1c}$ (NGSP %) in patients with type 2 diabetes (n=135,112) receiving multicomponent integrated care versus usual care. Team change, facilitated patient relay and patient education/self management have the largest effect size, expressed as mean difference (MD) with 95% confidence interval (CI). Similar changes are also reported for blood pressure and LDL-cholesterol. *N* is the number of trials (Lim LL et al Diabetes Care 2018).**




### *9.4 Change workflow and set up Diabetes Registers to deliver data-driven care*

As far back as 1990s, the IDF-Europe and WHO-Europe launched the St. Vincent's Declaration proposing structured data collection to detect microvascular complications (notably retinopathy and neuropathy) and improve care standard in people with T1D. This was soon followed by a similar initiative in Latin America (Diabetes Declaration of the Americas [DOTA]) where a standardised form was adopted by many countries in the region to establish registers (Qualidiab).[436] These initiatives provide useful learning on how to use data from these registers to identify care gaps and monitor outcomes.[437] Many of these T1D registers, such as the Pittsburgh Diabetes Register in the USA established in the early 1980s, have informed the world about the marked variations in terms of incidence and care standards, as well as the secular trends of complications (Figure 5A).[438]

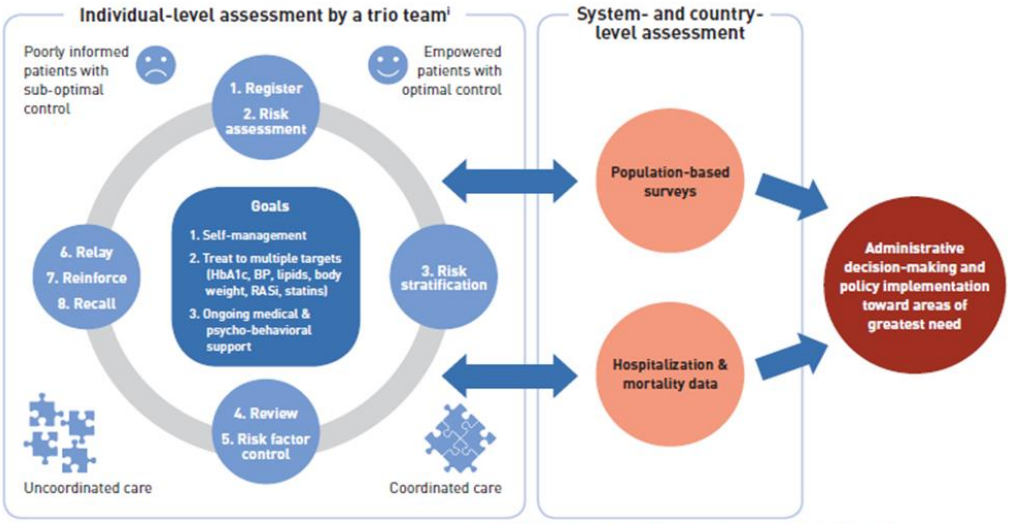
With the growing number of medications, most practice guidelines recommend periodic assessments of risk factors and comorbidities in order to individualise treatment targets and regimens.[247] To achieve these objectives, there is a need to establish a workflow to collect data systematically to stratify risk, triage care and personalise management. These diabetes registers, once established, can serve multiple purposes. On a patient level, the data can be used to provide feedback and individualise care. On a system level, these data can identify care gaps and benchmark performance. On a policy level, these data can be linked to population and hospitalisation data to identify root causes and monitor disease patterns and burden (Figure 12).[439]

Although not universally applicable, there are now institutional or national attempt to establish EMR systems by digitalising patient-related information collected during routine practice. These data management systems are usually well-designed, supported by good practices including privacy protection. Depending on the complexity of the system, the data types include demographics, hospitalisation, insurance claims and medications. These EMR systems can facilitate patient management including the 'pay for performance' schemes in England[440] and Taiwan in the field of diabetes.[441] Other workers have designed simple databases and change workflow to capture essential information during annual comprehensive assessment to set up diabetes registers for quality improvement. From a clinical perspective, once data are systematically collected, especially if relayed back to HCPs, patients and their caregivers, improvement in care standards often follows, in part due to improved awareness and self-management as well as intensified treatment with better adherence.[442]

### *9.5 A step-by-step implementation plan to deliver a data-driven integrated diabetes care plan*

Many countries are now adopting the WHO recommendation to provide universal health coverage including essential medicines (metformin, SU, insulin, statin, RASi, aspirin). However, to ensure the appropriate and effective use of these medicines, the health system needs 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.[443-446] Self-management, promoted by structured diabetes education, is the cornerstone of successful diabetes care.[260] In HICs, professional organisations have stipulated the credentials of educators and curriculum of diabetes self-management and education.[447] In LMICs and resource-constrained settings, trained physicians and nurses will need to take on the trainer and manager roles to transfer knowledge, develop care protocols, design workflows and train HCA to take on these assessment and education tasks, while doctors focus on making clinical decisions, prescribing drugs and looking after patients with more complex problems. In high-income areas, better care organisation with task shifting to facilitate team-based care can also lead to better efficiency and affordability with lower patient default rate and better job satisfaction for the workforce.[448]

**Figure 12. A schematic diagram showing how fragmented care can transform into data-driven, integrated diabetes care using a trio team including trained nurses and healthcare assistants, supervised by physicians, to collect data systematically during routine clinical practice to establish a register and use the data to empower self-management and treat to multiple targets with ongoing support. The data can be linked to population-based surveys and hospitalisation and mortality date for audit and surveillance purpose to influence policies and practices.**




International Diabetes Federation. IDF Diabetes Atlas, 9th Edition http://www.diabetesatlas.org/ accessed 2nd May 2020

Based on care models which are already in operation in some areas and in accordance with international guidelines,[247] members of this Commission have provided a template to help HCPs/planners/financers to initiate a structured and integrated assessment, education and support programme (Panel 2), which can be implemented even in low-resource settings. These integrated services can be supervised by physicians but implemented by non-physician personnel including nurses, HCA, trained college graduates or peers with diabetes, if nurses are in short supply (Figure 12).[448,449] In the last decade, a growing number of studies have demonstrated the effectiveness of structured patient education and support programmes delivered by trained community health workers/peers in underserved communities in HICs and to a lesser extent in LMICs.[450-452] In a systematic review of 118 randomised diabetes self-management education (DSME) programmes (defined as single, discrete DSME intervention with one or more follow-up assessment of $HbA_{1c}$ at 3-month interval or greater), contact time of 10 hours or more was associated with significant $HbA_{1c}$ reduction compared with exposure of less than 10 hours. More than 12 months of DSME intervention was more likely to achieve significant $HbA_{1c}$ reduction than those lasted ≤2.5 months. The benefit was most evident in those with $HbA_{1c}$>9% (75 mmol/mol), where intervention could lead to reduction of $HbA_{1c}$ as much as 0.7% (7.7 mmol/mol), with more than 70% of patients showing significant improvement.[453]

Panel 2 summarises the facilities, equipment and procedures required to deliver an integrated assessment, education and supporting service delivered by a trained nurse-HCA team including the time-scheduling of these sessions and person-hours required for a 'unit' of 800 patients. The panel stipulates how a typical week can be divided into sessions where non-physician personnel can be trained to gather clinical information, collect blood/urine samples and perform eye (e.g., visual acuity, fundus camera) or foot examination (e.g., sensation and pulses) to assess control of risk factors and detect complications. Depending on case complexity, a patient may need up to one hour to undergo a structured assessment at presentation and every 2–3 years thereafter for quality assurance. For newly-diagnosed patients, longer duration of education/contact time is recommended (e.g., 10 hours over 12 months in groups of 10)[453] are recommended. The content should include nature of disease, treatment targets, regular follow-up and monitoring, healthy lifestyles, medication adherence, sick day management and other special issues (e.g., planning for pregnancy, stress management). This can be followed by individualised sessions based on the risk profiles and needs of the patient.[260,454] Given a total of 3,840 person-hours of a nurse-HCA team, we estimated that 1,600 person-hours can be used to perform structured assessment and 1,200 person-hours for group education with the remaining 1,040 hours used

to provide additional support as needed (Panel 2). Once these patients are stabilised and educated, less time will be required and the team can then take on other tasks such as detecting individuals with undiagnosed or at risk of having diabetes, e.g., positive family history, obesity, history of gestational diabetes, polycystic ovary syndrome, hypertension, dyslipidaemia, NAFLD, smoking or high risk scores for early intervention.[365]

To maximise efficiency, clerical staff and/or HCA can be trained to perform simple measurements (e.g., BP, body weight, body height, waist circumference), collect biosamples (urine and blood), ask non-clinical questions (e.g., demographic data, 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 EMR. Alternatively, these databases can stand alone and periodically linked to other administrative databases for monitoring of outcomes. Even in areas without EMR, personal computers can be used to digitalise these paper-and-pen registers to enable patient recall every 2–3 years to avoid default and ascertain clinical outcomes including death.

Importantly, these 'structured' protocols for data-gathering together with continuing care by the same diabetes team with ongoing evaluation can facilitate on-the-job training and motivate members to champion these evidence-based care models.[323,455] Once 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 (e.g., young patients, elderly patients, patients with obesity, patients with multiple medications including insulin injections, patients with psychosocial stress or poor adherence).[456] In some settings, notably in LMICs pending healthcare investments and reforms, co-sharing of facilities and staff time for management of complex diseases (e.g., tuberculosis, HIV infection) can kick-start and expedite the formation of these diabetes teams to provide data-driven, integrated care for these diseases requiring long-term care.[167,457,458]

Due to the continuing nature of diabetes management encompassing prevention, diagnosis, treatment and rehabilitation and depending on the healthcare financing and workforce development in each country/area, these community-based diabetes teams with linkage to specialist-led Diabetes Centre should preferably have a predefined provider:patient ratio to avoid over- or under-utilisation of these resources. Based on existing models, we estimate that 0.25–0.50 physician supported by one nurse, one HCA and one clerical staff will be able to manage 800–1,600 patients on a recurring basis (depending on their risk profiles) as well as implement primary prevention programmes. The efficiency of this data-driven, integrated programme can be further enhanced using ICT, mobile health and peer support.

### *9.6 An example of using research-driven quality improvement initiatives to transform care and inform policies*

In Hong Kong, a research-driven quality improvement programme run by trained non-physician personnel, initiated at a university-affiliated hospital to overcome manpower shortage in early 1990s, evolved to become a territory-wide risk assessment and management programme.[459] Using 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. Based on 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 decision support to promote shared decision-making between patients and HCPs. Similar to the UKPDS Outcome Model,[460] data from the Hong Kong Diabetes Register were linked to hospitalisation records using unique identifier which 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 with display of trends of risk factor control and future risk of complications using bars and trend lines. These personalised data were accompanied by recommended treatment targets and decision support triggered by attained targets. By using technologically-assisted, data-driven integrated care, we can empower self-management, reduce clinical inertia, personalise care and monitor care quality. Through these regular assessments, the care

team can also identify patients with unstable control and complex phenotypes such as those with YOD, atypical presentations, emotional distress and frailty.[439,461] Thus, despite the large volume of patients and complex care protocols, it is possible to start improving the quality of care by using teams, logistics and data analytics to improve the efficiency and quality of care. By demonstrating better 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.[462,463]

In 2000, the hospital administrators created career paths for diabetes nurses to scale up the operation of these Diabetes Centres dedicated to providing assessment (eye, feet, blood/urine), education and care coordination. To date, in this city of 7.5 million population, 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, community-based primary care clinics offer similar risk assessment and management programme (RAMP-DM), enhanced by incorporation of the protocol of the JADE Programme.[464] In a 5-year evaluation analysis involving patients with 8 years of disease duration and without micro/macrovascular complications, the relative risk of any clinical event including death was reduced by 50% in the RAMP-DM participants, many of whom were also referred to a patient empowerment programme, compared with a propensity score-matched cohort.[465] In a subsequent cost-effectiveness analysis, the ARR of the RAMP-DM ranged from 3 to 13% and the NNT ranged from 7 to 68. Using existing infrastructures in the primary care setting and taking into account the implementation cost of USD 157 per individual including set up and ongoing cost, e.g., purchase of fundus camera, incorporating risk algorithms into the EMR and training nurses to perform the procedures and patient education, there was an average reduction of USD 7,000 over 5 years after considering all the costs incurred during hospital visits (consultations, drugs, investigations and procedures).[465] This cost-saving was due to the 2–9 times higher costs of these complications compared with the base costs.[466] Taken together, this territory-wide quality improvement initiative supports the clinical benefits and cost-saving nature of using information technology, logistics and data-driven integrated care, focusing on patient empowerment, feedback and treatment of multiple targets.[463]

Panel 3 shows a list of clinical and laboratory data which can be collected periodically and the JADE risk stratification and care model which has been adapted by the aforementioned territory-wide RAMP-DM with proven benefits and cost-effectiveness.[464,467] By documenting these risk profiles at presentation and every 18–24 months thereafter, we 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. These diabetes registers when linked to EMR/hospitalisation data or other disease registers (e.g., ESKD, myocardial infarction, cancer, death) using a unique identifier 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 within- and between-country differences in causes, trajectories and consequences of diabetes. By using attainment of treatment targets, access to structured education programmes and prescription of organ-protective drugs as performance indexes for benchmarking purposes, we can also promote best practices. These real-world effectiveness data complement efficacy data from RCTs in controlled settings[278,468] to guide clinical practice, as well as identify subgroups most likely to benefit or develop adverse events.[439,469]

### *9.7 Use Specialised Diabetes Centres to promote research and professional education*

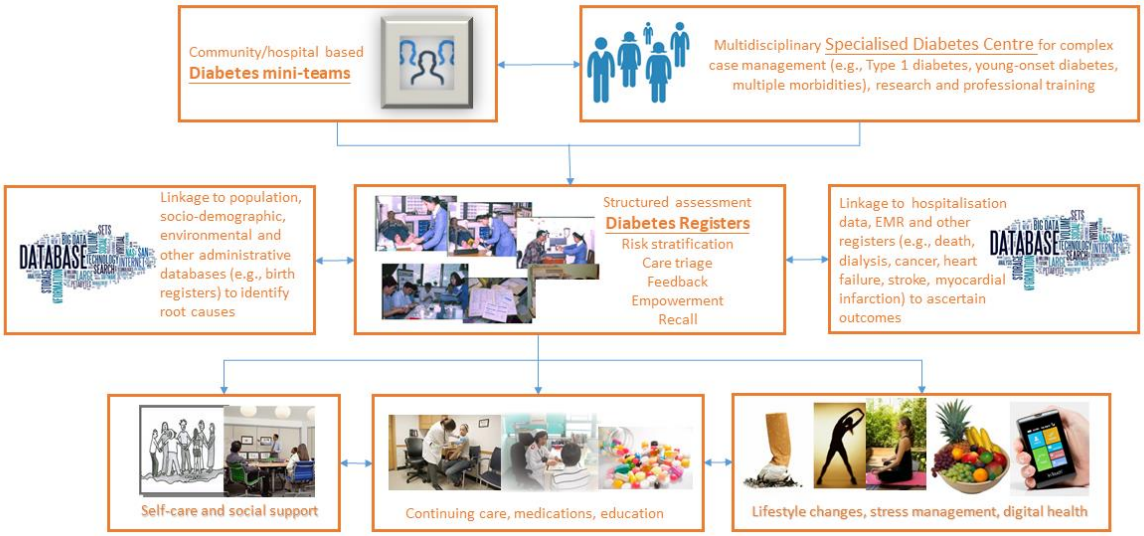
Professional education is a prerequisite to good clinical care and effective patient education. Using insulin treatment as an example, large-scale audits often revealed inappropriate use of insulin (timing, regimen, dosages) by untrained HCPs with adverse consequences. In real-world practice, there are considerable delays in the initiation and intensification of insulin, with a lag period of 4–8 years in patients with T2D, resulting in prolonged exposure to hyperglycaemia.[470] Even if insulin is initiated, lack of titration and self-discontinuation are not uncommon. Inappropriate insulin regimens and excessive use of blood glucose lowering drugs can cause severe hypoglycaemia, which is a leading cause of emergency hospitalisation especially in the elderly.[241] Patients with multiple morbidities and polypharmacy will need periodic review of their medications to ensure safety.[471] In the cluster-randomised 'Stepping up' Program conducted in Australia, an accredited diabetes nurse educator served

as mentor and trained nurses working in primary care clinics to initiate and titrate insulin in patients with T2D who needed insulin therapy. Compared with the 'control clinics', 70% of patients managed by these trained nurses in the 'intervention clinics' were started on insulin compared with 22% in the 'control clinics' with a 0.6% (6.6 mmol/mol) difference in $HbA_{1c}$ in favour of the 'intervention clinics'.[472]

Diabetes management has now become increasingly complex with many technological advancements, such as the use of multiple medications and injectables, continuous glucose monitoring, insulin delivery systems and metabolic surgery. There are also emerging technologies such as using biogenetic markers in precision medicine.[473] To ensure that patients get the full benefits of these advancements, there is a need to expand the curriculum of undergraduate programmes with ongoing postgraduate and professional training in diabetes and other NCDs. Attending regular conferences organised by professional organisations is essential for updating professional knowledge in order to improve care. Besides, hospital- or community-based specialised Diabetes Centres, often affiliated with academic institutions or major healthcare organisations are in a good position to set up accreditation programmes in diabetes management and education (e.g., Certificate, Diploma or Master courses). These programmes will help build a critical 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[247] including the IDF.[389,474]

These Centres, whether based in LMICs or HICs, should have a dedicated space led by one or more physicians with credentials in diabetes management and nurses with training in diabetes education supported by appropriate equipment and tools (Panel 2). These Centres are usually tasked with management of patients with complex needs, such as T1D, YOD, MODY, T2D with comorbidities including depression, supported by other healthcare professionals (e.g., dietitians and podiatrists) and specialists (e.g., ophthalmologists, metabolic surgeons, cardiologists, nephrologists, psychiatrists) and work closely with primary care physicians to provide collaborative care. For quality improvement and research purposes, these Centres are recommended to establish registers and ensure patients are seen at the right time by the right team in the right setting to achieve the best outcome.[415] By combining practice, research and professional training, these Centres can take on additional roles of monitoring performance, analysing registers and developing new programmes to address unmet needs (Figure 13). In a prospective cohort of 7,488 patients with T2D (1986–1991) followed up in Italy, patients seen only by family physicians had a higher mortality than the general population with a SMR of 1.62 (95% CI 1.51–1.74). This fell to 1.44 (1.34–1.54) among patients attending both family physicians and Diabetes Centres. The respective 5-year survival probabilities were 0.76 (0.75–0.78) and 0.81 (0.80–0.82) compared with the general population. Attending the Diabetes Centres was an independent predictor of improved survival, after adjusting for sex, age and diabetes therapies. Similar benefits were observed for cardiovascular death.[475,476]

**Figure 13. A schematic diagram showing the combined use of Specialised Diabetes Centres, diabetes teams and diabetes 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.**



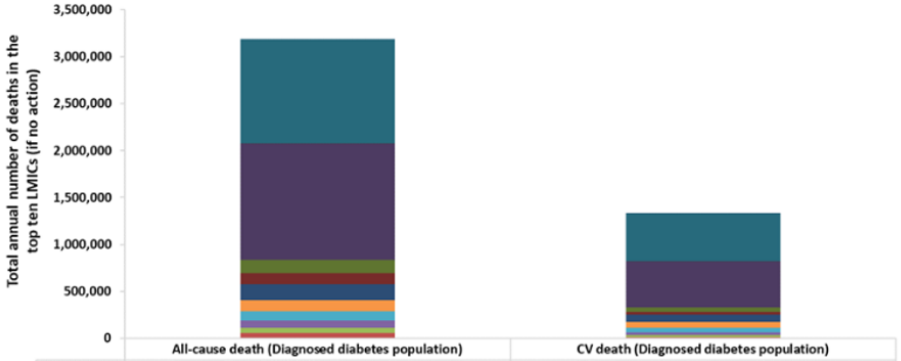

## 10 Use simulation models to estimate and compare the impacts of 'no action' versus 'action'

In this evidence-based document, we put great emphasis on the inter-dependency of society, community and individuals in influencing outcomes. In the case of T1D, we have quantified the impacts of provision of comprehensive care in reducing premature death in young individuals (Section 6.4). For T2D, rapid societal changes have changed our ecosystem, way of living and access to care especially in LMICs, which explain a large fraction of the epidemic, albeit potentially preventable. The health consequences of this epidemic will in turn have societal consequences, notably healthcare expenditure, societal productivity and quality of life. The complex pathophysiology of diabetes has led to many faces of diabetes while individuals with diabetes and those at risk have many needs, beyond medical. Over the last three decades, we have gathered a wealth of data regarding the size of the problem and effects of potential solutions. In the current section, we have used these data to develop two models to quantify the burden of diabetes and the impacts of an integrated prevention and care programme in T2D. The methodologies of these models are detailed in the Supplemental Materials. These models are available on line to allow readers to enter local data and estimate potential effects of implementing various strategies in their countries/areas, organisations and/or clinic practices.

### *10.1 Use IDF, WHO and RCT data to estimate the effects of care access on reducing death and CVD in T2D*

To quantify the impact of this integrated society-community-individual strategy (Figure 10), we compared the effects of 'no action' versus 'action' by reducing multiple risk factors. We first used the 2016 WHO Global Health Estimates on causes of death[11] and 2017 IDF World Diabetes Atlas on diabetes prevalence in the 30–69 age group.[3] We then used the hazard ratios of all-cause (1.8) and CVD-related deaths (2.3) associated with diabetes (including diagnosed and undiagnosed) versus those without diabetes as reported in the Emerging Risk Factor Collaborative Cohort,[1] to estimate the total number of deaths attributable to diabetes (refer to Supplemental Material for details of methodology). Based on these assumptions, we selected the top 10 LMICs with the largest population with diabetes, which account for 50% of the global diabetes population. We modelled that amongst these 109 million individuals (aged 30–69 years) diagnosed with diabetes living in these 10 LMICs, an estimated 3.2 million individuals die after 3 years, of whom 1.3 million would be due to CVD (Figure 14).

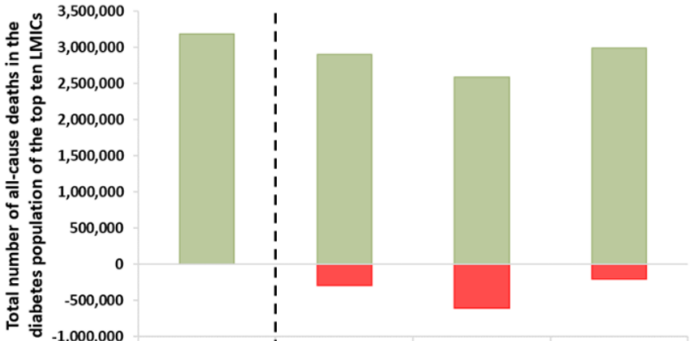
**Figure 14. 3-year estimation of all-cause and CV-death in people with diagnosed diabetes (aged 30-69 years) in the top ten LMICs using WHO and IDF data (2017) and estimated HR of 1.8 (all-cause death) and 2.32 (CV-death) for diabetes based on the Emerging Risk Factors Collaboration.**




| | All-cause death (Diagnosed diabetes population) | CV death (Diagnosed diabetes population) |
|---|---|---|
| China | 1,111,194 | 507,880 |
| India | 1,239,506 | 497,537 |
| Brazil | 140,759 | 46,353 |
| Mexico | 118,833 | 26,055 |
| Indonesia | 173,452 | 80,204 |
| Egypt | 118,609 | 60,875 |
| Pakistan | 99,834 | 49,808 |
| Bangladesh | 74,289 | 31,653 |
| Turkey | 56,205 | 18,585 |
| Thailand | 56,355 | 13,252 |
| Total | 3,189,035 | 1,332,200 |

The use of statins which are available at extremely low costs for generic preparations (even in LMICs) to reduce LDL-cholesterol by 1 mmol/L (39 mg/dL) can lower the risk of all-cause death by 9%[477] and CVD and related death by 13%,[211] especially in patients with diabetes with either high cardiovascular risk or LDL-cholesterol ≥2.6 mmol/L (100 mg/dL). While reducing $HbA_{1c}$ by 1% (11 mmol/mol) may lower CVD events[208] or cardiovascular death by 10%[209] and reducing systolic BP by 10 mmHg by 20%[210], we estimate that each of these interventions can reduce CVD and/or all-cause death by 10–20% (Table S1). Although the levels of $HbA_{1c}$, BP and LDL-cholesterol are not known in these populations, we assume that the majority of diagnosed individuals with diabetes can benefit from further reduction in risk factors. Assuming a diagnosis rate of 50% and by ensuring access to essential medicines including statins, blood glucose and BP-lowering drugs in at least 70% of these diagnosed individuals, together with a supporting system to ensure sustained reduction of these risk factors for three years, we can potentially avert between 300,000 and 600,000 premature deaths by reducing BP by 10 mmHg, depending on their baseline BP. By treating them with statins to reduce LDL-cholesterol by 1 mmol/L (39 mg/dL), we can avert another 200,000 all-cause deaths, thereby averting up to 800,000 premature deaths (Figure 15A). By improving each of these three risk factors ($HbA_{1c}$, LDL-cholesterol and BP), we can potentially avert between 30,000 and 240,000 cardiovascular deaths depending on their baseline risk factors (Figure 15B).

**Fig 15A. 3-year estimation of total number of all-cause deaths with status quo and all-cause deaths averted with interventions in the diagnosed diabetes population aged 30-69 years from the top 10 LMICs**




| | No-Action | SBP -10mmHg | SBP -10 mmHg (SBP≥140) | LDLC -1 mmol/L |
|---|---|---|---|---|
| Deaths_Total | 3,189,035 | 2,898,833 | 2,586,307 | 2,988,126 |
| Deaths_Averted | | -290,202 | -602,728 | -200,909 |
| DM population | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) No change in diabetes prevalence and death rate for 3 years; 4) Death rate = birth rate; 5) Sustained effect size for 3 years*

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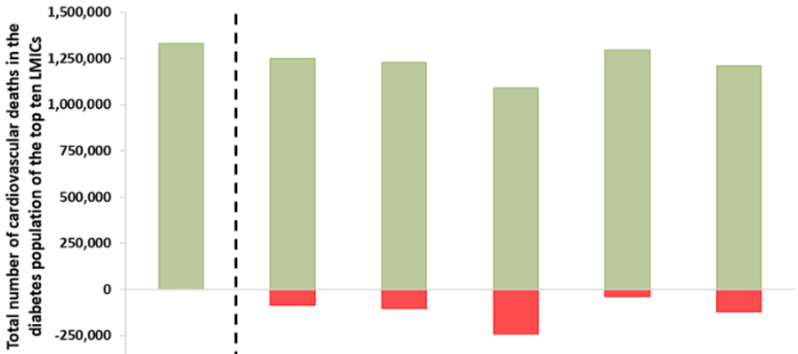
**Fig 15B. 3-year estimation of total number of CV deaths with status quo and CV deaths averted with interventions in diagnosed diabetes population aged 30-69 years from the top 10 LMICs**




| | No-Action | A1C -0.9% | SBP -10mmHg | SBP -10 mmHg (SBP≥140) | SBP -10 mmHg (SBP<140) | LDLC -1 mmol/L |
|---|---|---|---|---|---|---|
| Deaths_Total | 1,332,200 | 1,248,272 | 1,229,621 | 1,089,740 | 1,294,899 | 1,210,970 |
| Deaths_Averted | | -83,929 | -102,579 | -242,460 | -37,302 | -121,230 |
| DM population | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) No change in diabetes prevalence and death rate for 3 years; 4) Death rate = birth rate; 5) Sustained effect size for 3 years*

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### *10.2 Use observational data to develop a risk calculator and use RCT data to estimate effects of intervention*

Each person with diabetes is unique with different risk factors, trajectories, complications and outcomes which can be modified by improving access to care, education and medications, as well as changing behaviours and social habits.[478] In our literature search, there are very few country/territory-wide registers with comprehensive data including non-modifiable (e.g., age, sex, duration of diabetes, complications) and modifiable risk factors (e.g., $HbA_{1c}$, BP, LDL-cholesterol, BMI, use of tobacco, self-management, lifestyles) linked to clinical outcomes. Some of these registers come from small countries or areas such as Sweden and Hong Kong, in part due to their small population size. In these countries/areas, the linkage of clinical records to national disease registers or EMR/hospitalisation records can be facilitated by unique identifiers and the use of International Classification of Diseases (ICD) codes.[59,479] Similar to the UKPDS Outcome Model including risk equations based on data collected in a RCT setting,[460,480] risk equations can be developed using these real-world databases, although its external validation may be confounded by ethnicity, locally-relevant risk factors and care standards.[481,482] That said, these models with absolute risk prediction, can provide useful information

regarding the effects of reducing different risk factors using different strategies which can help HCPs or planners prioritise their action plans.

### *10.3 Use $HbA_{1c}$, BP, LDL-cholesterol to develop an 'ABC' model and estimate effects of integrated care in 3 years*

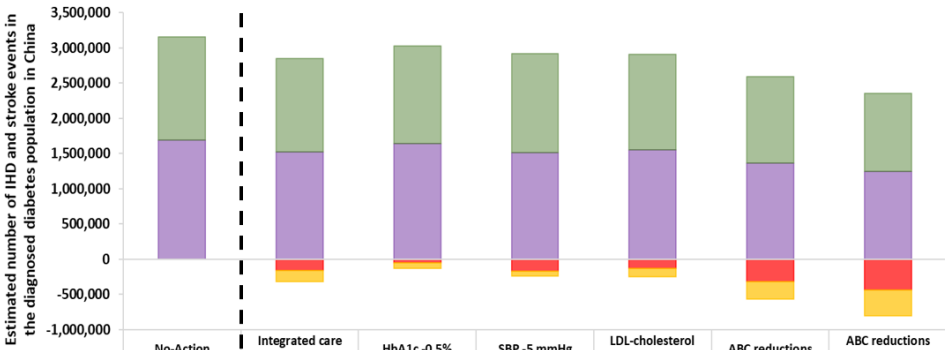
Although we have curated 40 cross-sectional surveys to provide a global landscape of risk factor distribution in 1.9 million people with T1D or T2D, most of these surveys reported only basic information and did not have details on cardiovascular complications and renal function which are important prognostic factors (Figure 6). We therefore used commonly reported variables (age, sex, duration of diabetes, use of tobacco, $HbA_{1c}$, systolic/diastolic BP, LDL-cholesterol and BMI) available in the Hong Kong Diabetes Register and the JADE Register consisting of 22,514 patients with T2D (1994–2015) observed for 65,966 patient-years since 1994,[483]and used Poisson regression analysis[484] to develop an 'ABC' model to estimate the incidence of CVD (including ischaemic heart disease and stroke) and related death up to 3 years.

We externally validated this model by using the published summary data of two prospective cohorts with reported events. These included the Hong Kong Diabetes Database consisting of 212,659 Chinese patients with T2D and the National Swedish Diabetes Register consisting of 96,673 with imputed data for 271,174 non-Chinese patients with T2D (Table S2). By simulating one million patients with similar profile, the ABC model performed well with risk ratio of predicted versus observed events approaching 1 (Table S3). Using this validated model, we can estimate the 3-year incidence rate of CVD in diabetes populations (aged 20-79 years) with different combinations of risk factors. We then estimated the impact of reducing each or all three ABC risk factors using the RRR reported in RCTs[208-211] (Table S1) based on medications alone with or without provision of integrated care,[275] the latter aimed at overcoming clinical inertia and non-adherence.[268]

We selected two published cohorts with data needed to run the ABC model. In the China NCD Surveillance Cohort which included predominantly newly-diagnosed individuals,[485] the mean $HbA_{1c}$ was 7.2% (55 mmol/mol), systolic BP, 144 mmHg and LDL-cholesterol, 2.59 mmol/L (100 mg/dL). In China, 10% of adults have diabetes.[381] Assuming a 50% diagnosis rate (57 million) with risk profiles similar to the China NCD Surveillance Cohort,[485] with 70% of these diagnosed patients under usual care, we estimated that 3 million of them may develop a CVD 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 BP by 2.4 mmHg, and LDL-cholesterol by 0.14 mmol/L (5.4 mg/dL)[275] to at least 70% of these diagnosed individuals, we could avert 300,000 CVD events.

If we intensify control of risk factors using medications to lower $HbA_{1c}$ by 0.5% (5.5 mmol/mol), LDL-cholesterol by 0.5 mmol/L (19 mg/dL) and systolic BP by 5 mmHg, we could avert between 130,000 and 250,000 CVD events. If all three risk factors are improved, we can avert 570,000 CVD events which increases to 800,000 events if this is combined with integrated care (Figure 16A). We used the published costs of diabetic complications in a public healthcare setting in Hong Kong[466] adjusted for cost of living index, we estimated the potential cost saving in these scenarios (refer to Supplemental Material). If status quo is maintained, these CVD events will cost the system over USD 5,200 million which can be reduced by USD 1,300 million if care is organised along with increased use of medications to reduce multiple risk factors (Figure 16B).

**Fig 16A. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (community-based): Estimated incidence of ischaemic heart disease (IHD )and stroke, and events averted with interventions**




| | No-Action | Integrated care (IC) | HbA1c -0.5% | SBP -5 mmHg | LDL-cholesterol -0.5 mmol/L | ABC reductions | ABC reductions combined with IC |
|---|---|---|---|---|---|---|---|
| IHD_Incidence | 1,470,865 | 1,321,440 | 1,382,673 | 1,407,115 | 1,350,582 | 1,221,214 | 1,108,020 |
| STK_Incidence | 1,686,567 | 1,522,873 | 1,640,356 | 1,514,673 | 1,555,308 | 1,367,432 | 1,247,987 |
| IHD_Averted | | -149,425 | -88,191 | -63,750 | -120,283 | -249,651 | -362,845 |
| STK_Averted | | -163,695 | -46,211 | -171,894 | -131,259 | -319,135 | -438,581 |
| Total_Incidence | 3,157,432 | 2,844,312 | 3,023,030 | 2,921,787 | 2,905,890 | 2,588,645 | 2,356,007 |
| Total_Averted | | -313,120 | -134,402 | -235,644 | -251,542 | -568,786 | -801,425 |
| DM Population | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. ABC refers to Hb**A**$_{1c}$, systolic **B**lood pressure and LDL-**C**holesterol.*

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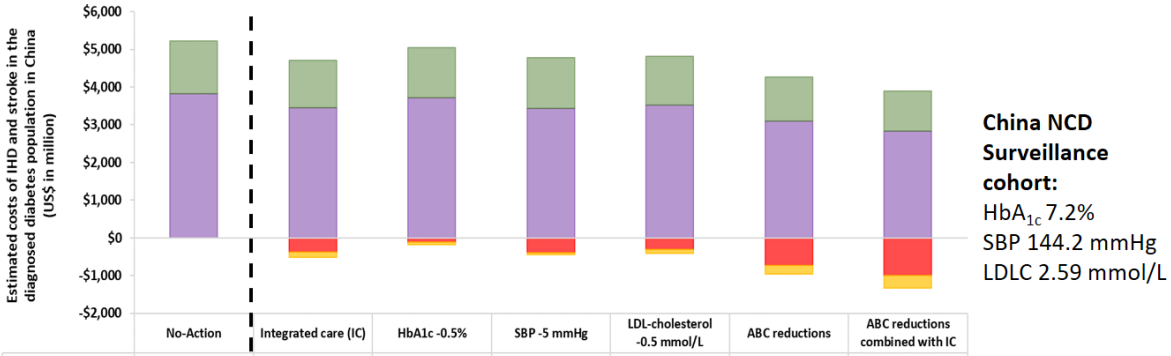
**Fig 16B. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (community-based): Estimated costs incurred and saved for ischaemic heart disease (IHD) and stroke with interventions**




| | No-Action | Integrated care (IC) | HbA1c -0.5% | SBP -5 mmHg | LDL-cholesterol -0.5 mmol/L | ABC reductions | ABC reductions combined with IC |
|---|---|---|---|---|---|---|---|
| IHD_cost incurred | $1,399 | $1,257 | $1,315 | $1,338 | $1,285 | $1,162 | $1,054 |
| Stroke_cost incurred | $3,829 | $3,457 | $3,724 | $3,438 | $3,531 | $3,104 | $2,833 |
| IHD_cost saved | | -$142 | -$84 | -$61 | -$114 | -$237 | -$345 |
| Stroke_cost saved | | -$372 | -$105 | -$390 | -$298 | -$724 | -$996 |
| Total_cost incurred | $5,228 | $4,714 | $5,039 | $4,777 | $4,815 | $4,266 | $3,887 |
| Total_cost saved | | -$514 | -$189 | -$451 | -$412 | -$962 | -$1,341 |

a. *The combined public and private direct medical costs per event in China: US$ 951 for CHD, US$ 2,270 for stroke (assumed no baseline complications).*
b. *CKD, ESRD and PVD are excluded in the calculation and thus, these are underestimations. *Integrated care (task shifting).*
c. *Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. ABC refers to Hb**A**$_{1c}$, systolic **B**lood pressure and LDL-**C**holesterol.*

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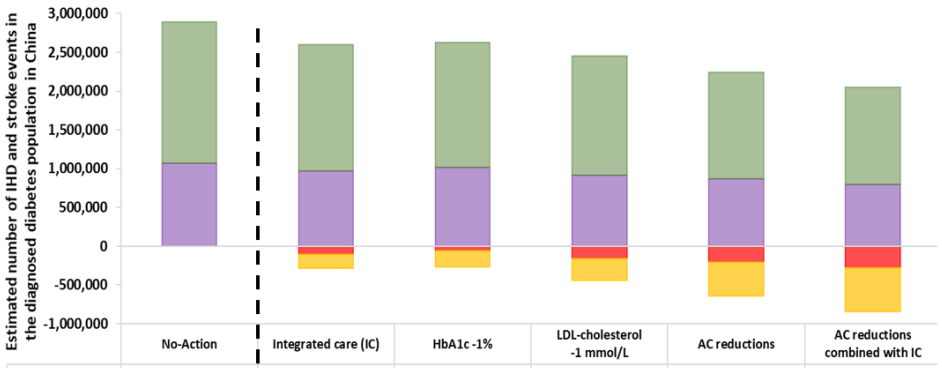
In a clinic-based cohort of Chinese patients with T2D enrolled in the JADE Register,[486] the mean disease duration was 5 years. Compared with the China NCD Surveillance Cohort,[485] these patients had better BP control but higher $HbA_{1c}$ and LDL-cholesterol levels ($HbA_{1c}$ 7.9% [63 mmol/mol], BP 125.8 mmHg, LDL-cholesterol 2.94 mmol/L [114 mg/dL]). Assuming a 50% diagnosis rate with similar risk profiles, if we can reduce $HbA_{1c}$ 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 CVD events and USD 1,400 million will be saved (Figure 17A/B).

**Fig 17A. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (clinic-based): Estimated incidence of ischaemic heart disease (IHD) and stroke, and events averted with interventions**



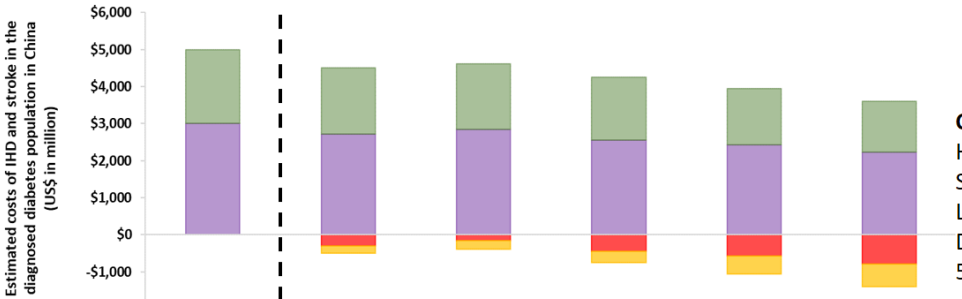

**China JADE study:**
$HbA_{1c}$ 7.9%
SBP 125.8 mmHg
LDLC 2.94 mmol/L
Disease duration
5 years

| | No-Action | Integrated care (IC) | HbA1c -1% | LDL-cholesterol -1 mmol/L | AC reductions | AC reductions combined with IC |
|---|---|---|---|---|---|---|
| IHD_Incidence | 1,818,568 | 1,634,014 | 1,610,119 | 1,538,509 | 1,375,918 | 1,255,538 |
| Stroke_Incidence | 1,075,112 | 970,671 | 1,017,148 | 917,071 | 871,279 | 795,126 |
| IHD_Averted | | -184,554 | -208,450 | -280,060 | -442,650 | -563,031 |
| Stroke_Averted | | -104,441 | -57,964 | -158,042 | -203,833 | -279,987 |
| Total_Incidence | 2,893,681 | 2,604,686 | 2,627,267 | 2,455,580 | 2,247,197 | 2,050,663 |
| Total_Averted | | -288,995 | -266,414 | -438,101 | -646,484 | -843,018 |
| DM Population | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. AC refers to Hb**A**$_{1C}$ and LDL-**C**holesterol.*



**Figure 17B. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (clinic-based): Estimated costs incurred and saved for ischaemic heart disease (IHD) and stroke with interventions**




**China JADE study:**
$HbA_{1c}$ 7.9%
SBP 125.8 mmHg
LDL-C 2.94 mmol/L
Disease duration
5 years

| | No-Action | Integrated care (IC) | HbA1c -1% | LDL-cholesterol -1 mmol/L | AC reductions | AC reductions combined with IC |
|---|---|---|---|---|---|---|
| IHD_cost incurred | $1,999 | $1,796 | $1,770 | $1,691 | $1,512 | $1,380 |
| Stroke_cost incurred | $3,004 | $2,712 | $2,842 | $2,563 | $2,435 | $2,222 |
| IHD_cost saved | | -$203 | -$229 | -$308 | -$487 | -$619 |
| Stroke_cost saved | | -$292 | -$162 | -$442 | -$570 | -$782 |
| Total_cost incurred | $5,003 | $4,509 | $4,612 | $4,254 | $3,947 | $3,602 |
| Total_cost saved | | -$495 | -$391 | -$749 | -$1,056 | -$1,401 |

a. *The combined public and private direct medical costs per event in China: US$ 1,099 for CHD, US$ 2,794 for stroke (assumed no baseline complications).*
b. *CKD, ESRD and PVD are excluded in the calculation and thus, these are underestimations. *Integrated care (task shifting).*
c. *Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. AC refers to Hb**A**$_{1C}$ and LDL-**C**holesterol.*



We acknowledge the considerable inter-country variations in healthcare financing (public, private, partially subsidised) and provider systems (single care provider versus multiple care providers). However, based on published epidemiological and RCT data, this case study illustrates the potential impacts of improving access to medications, continuing care and patient education at a system level, which can prevent millions of CVD events and save billions of dollars. In this case study, 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 Chinese with different risk profiles in both public and public-private partnership settings.[57,459] 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 amongst the affected workforce.

### *10.4 Use a simulation model to estimate the impact of a 20-year society-community-individual T2D prevention strategy*

We developed a simple Markov microsimulation model[204] to evaluate the short-, mid- and long-term impact of an integrated strategy for preventing T2D and CVD, compared with a status quo or non-intervention. This multicomponent strategy include education-social-environmental policies, population-based health promotion policies as well as early detection, prevention and treatment programs. The model was developed for meeting the particular need of this Report, i.e., the model needs to be:

1. flexible for applying the model in a diverse country setting
2. less data-demanding and make use of data available in most countries especially low-income countries and
3. able to capture the main health impact of the preventive programmes (refer to Supplemental Material).

Using published data from China,[487] Hong Kong[488] and Brazil,[364] we estimate the distribution of risk categories for progression to T2D and the number of T2D and CVD events averted if a hypothetical multicomponent intervention is implemented in one million individuals in 5, 10 and 20 years compared to 'status quo'. The total effect size of this society-community-individual strategy[489] is inferred from the relative risks associated with modifiable risk factors reported in observational studies (Table 2) and RCTs using lifestyle interventions and medications (Table 4).

Assuming the best scenario where governments, regulators, funders, practitioners, industry and community act in concert to transform the ecosystem and establish community-based facilities to raise awareness and identify high-risk individuals for early intervention with linkage to an integrated healthcare system, we can create maximal impacts at all levels to reduce T2D and CVD events in a 20-year horizon. We assume that a societal strategy will reduce the risk of progression from low risk to high risk for diabetes by 5% while a combined population- and individual-based approach will reduce the risk of progression to T2D and CVD both by 25%. Based on reports from population-based surveys,[364] we assume the annual incidence of diabetes in the high risk group (e.g. prediabetes, metabolic syndrome) to be 1.9%, 3.8% and 3.8% in the <45, 45-60 and >60 age groups, respectively. The corresponding figures for annual progression from low to high risk for diabetes are 5, 8 and 10%. The annual incidence of CVD is estimated from the 2013 American College of Cardiology/American Heart Association Atherosclerosis Cardiovascular Disease (ACC/AHA ASCVD) risk equation using common risk factors including age, sex, smoking, lipids, $HbA_{1c}$ and BMI.[490]

1) Societal strategy
   a) Universal secondary school education
   b) Social inclusion and protection
   c) Environmental protection

2) Population-based health-promoting strategy
   a) Health awareness programme (e.g., public education, social media)
   b) Tobacco control (e.g., price, smoke-free area, media, warnings, tax, cessation support)
   c) Food policies (e.g., price, adverts, labelling, tax, media)
      i) ensure food security
      ii) avoid foods with high sugar, salt, trans fat content
      iii) provide subsidy for healthy foods

3) Community-based detection and prevention programme
   a) Universal health coverage
   b) Strong primary care system
   c) Use risk conditions and risk scores to identify high-risk individuals for primary prevention
   d) Use non-physician personnel to implement diabetes prevention programmes
   e) Use technology to increase reach, effectiveness, adoption and maintenance of diabetes prevention programmes

f) Early use of metformin, RASi and statins in high-risk individuals to prevent T2D and/or CVD

The model estimates the total and cumulative effects of these health policies and system change over a 20-year horizon. The impact of the high-risk population-based strategy such as intensive lifestyle intervention or metformin use applies to the high-risk population for T2D. Early use of organ-protective drugs such as statins and RASi applies to the high-risk population for CVD (e.g., hypertension, obesity, dyslipidaemia). The impact of whole population strategies such as tobacco control, sugar-sweetened beverage tax applies to all groups for reduction of risk factors. The strengthening of healthcare system through capacity building enables early detection and intervention of these high-risk individuals once diagnosed. In support of this multicomponent strategy, there is now evidence suggesting that prevention of T2D will translate into long-term reduction of CVD.[256] While reducing multiple risk factors using statins and RASi can prevent the risk of CVD by 20–40% in high-risk individuals with or without T2D,[372] the implementation of integrated diabetes care can reduce CVD events by 50%.[459]

Figure 18A/B show the distribution of risk factors in a Chinese population stratified by age groups, as well as the estimated rates of progression to prediabetes and T2D in different age groups based on prior knowledge.[487,488] Assuming that we can successfully implement all components within this strategy in an integrated manner, in the next 10 years, for every one million adults, we can avert 22,489 diabetes events and 17,270 CVD events which will increase to 33,733 and 51,863, respectively after 20 years. These figures translate to prevention of T2D in 44 million adults and that of CVD events in 67 million adults for a 1.3 billion population in China alone. Using the same arguments, Figure 19A/19B show similar impacts in Brazil in a population of 130 million in 2017.

**Figure 18A. Risk factor distribution in 1 million Chinese population and using risk equations to project diabetes/CVD events with or without an integrated society-community-individual strategy aimed at improving health environment, reducing population risk and implementing structured lifestyle modification in high risk individuals**

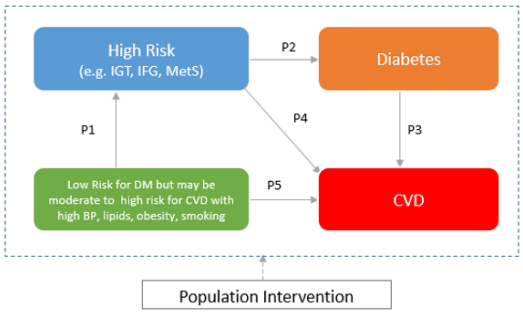


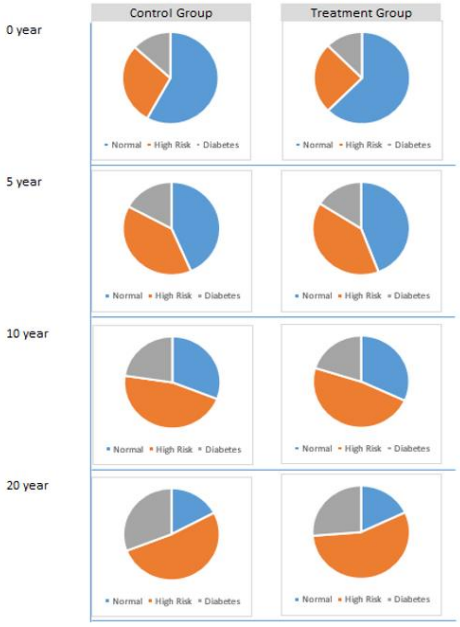

Table 1. Required information for population distribution

| Input Parameters | Age Groups | | |
|---|---|---|---|
| Baseline Demographics | <45 | 45~65 | >65 |
| Number of person to intervene | 300,000 | 300,000 | 400000 |
| Proportion of High Risk persons in the intervention population | 10% | 20% | 40% |
| Proportion of Diabetes in the intervention population | 5% | 10% | 20% |
| Proportion of Smokers in the intervention population | 30% | 30% | 30% |
| Annual probability of developing diabetes amongst those at high risk for diabetes | 1.3% | 3.8% | 3.8% |
| Annual probability of moving to high risk amongst those at low risk for diabetes | 5% | 8% | 10% |

Table 2. Specify the baseline values for diabetes and CVD for the intervention population

| Normal Risk | <45 | 45~65 | >65 |
|---|---|---|---|
| Average HbA1c | 5.5% | 5.5% | 5.5% |
| Average BMI | 21.6 | 23.3 | 23.1 |
| Average SBP | 110 | 119 | 118 |
| Average Total Cholesterol | 4.23 | 4.56 | 4.53 |
| Average HDL-C | 1.30 | 1.30 | 1.30 |
| High Risk | | | |
| Average HbA1c | 6.0% | 6.0% | 6.0% |
| Average BMI | 23 | 25 | 25 |
| Average SBP | 119 | 129 | 128 |
| Average Total Cholesterol | 4.63 | 4.39 | 4.35 |
| Average HDL -C | 1.30 | 1.30 | 1.30 |
| Diabetes | | | |
| Average HbA1c | 8.5% | 8.0% | 7.5% |
| Average BMI | 23 | 25 | 25 |
| Average SBP | 124 | 134 | 133 |
| Average Total Cholesterol | 4.68 | 5.05 | 5.01 |
| Average HDL-C | 1.24 | 1.24 | 1.24 |

**Figure 18B. 20-year projection of diabetes and CVD events in 1 million people in China with or without an integrated society-community-individual strategy.**




| Simulation Results | | |
|---|---|---|
| Number of Diabetes Prevented * | Events | Relative Risk Reduction |
| 5 years | 11065 | 75.33% |
| 10 years | 22489 | 76.24% |
| 20 years | 33773 | 76.43% |
| Number of CVD Prevented * | Events | Relative Risk Reduction |
| 5 years | 6617 | 75.37% |
| 10 years | 17270 | 76.14% |
| 20 years | 51863 | 79.53% |

* (Control-Intervention)

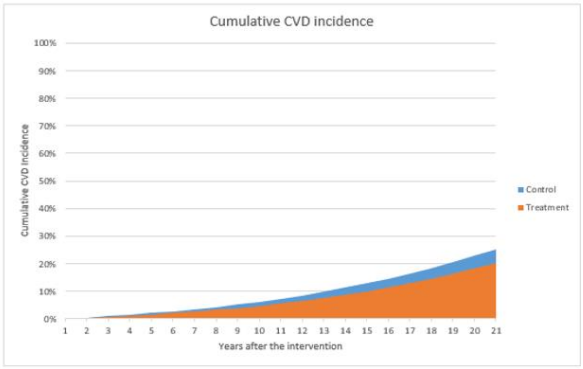



**Figure 19A. Risk factor distribution in 1 million Brazilian population and using risk equations to project diabetes/CVD events with or without an integrated society-community-individual strategy aimed at improving health environment, reducing population risk and implementing structured lifestyle modification program in high risk individuals**

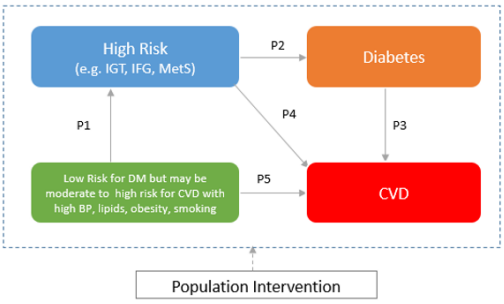


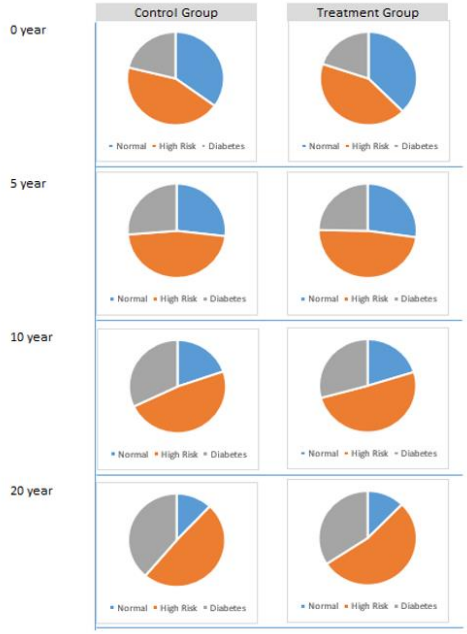

Table 1. Required information for population distribution

| Input Parameters | Age Groups | | |
|---|---|---|---|
| Baseline Demographics | <45 | 45~65 | >65 |
| Number of person to intervene | 300,000 | 300,000 | 400000 |
| Proportion of high risk persons in the intervention population | 34% | 44% | 48% |
| Proportion of diabetes in the intervention population | 6% | 19% | 31% |
| Proportion of smokers in the intervention population | 10% | 14% | 9% |
| Annual probability of developing diabetes amongst those at high risk for diabetes | 1.9% | 3.8% | 3.8% |
| Annual probability of moving to high risk amongst those at low risk for diabetes | 5% | 8% | 10% |

Table 2. Specify the baseline values for diabetes and CVD for the intervention population

| Normal Risk | <45 | 45~65 | >65 |
|---|---|---|---|
| Average HbA1c | 5.07% | 5.18% | 5.31% |
| Average BMI | 25 | 25 | 25 |
| Average SBP | 112 | 117 | 127 |
| Average Total Cholesterol | 5.19 | 5.63 | 5.63 |
| Average HDL-C | 1.5 | 1.6 | 1.7 |
| High Risk | | | |
| Average HbA1c | 5.18% | 5.30% | 5.38% |
| Average BMI | 27 | 28 | 27 |
| Average SBP | 118 | 123 | 131 |
| Average Total Cholesterol | 5.41 | 5.72 | 5.56 |
| Average HDL-C | 1.4 | 1.4 | 1.5 |
| Diabetes | | | |
| Average HbA1c | 6.50% | 6.70% | 6.60% |
| Average BMI | 31 | 29 | 28 |
| Average SBP | 122 | 129 | 135 |
| Average Total Cholesterol | 5.43 | 5.62 | 5.27 |
| Average HDL-C | 1.29 | 1.37 | 1.38 |

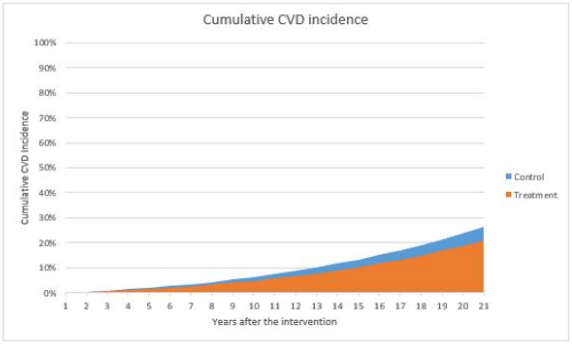
**Figure 19B. 20-year projection of diabetes and CVD events in 1 million people in Brazil with or without an integrated society-community-individual strategy.**




Simulation Results

| Number of Diabetes Prevented * | Events | Relative Risk Reduction |
|---|---|---|
| 5 years | 14407 | 76.01% |
| 10 years | 24564 | 77.38% |
| 20 years | 27997 | 77.83% |
| **Number of CVD Prevented *** | **Events** | **Relative Risk Reduction** |
| 5 years | 6855 | 75.38% |
| 10 years | 17892 | 76.18% |
| 20 years | 52991 | 79.78% |

* (Control-Intervention)




## 11 Use unified data management to track disease burden, measure impacts and inform policies

The total prevalence of diabetes reflects disease burden; age-sex specific prevalence rates allow 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 T2D may reflect impacts of interventions amongst other factors. The latter include but are not limited to, political, socioeconomical and technological changes within a population and/or area. Given the silent and progressive nature of diabetes and its complications, in this section, we discussed the utility of using prospectively designed and unified data management systems to support the collective needs of clinical, surveillance and research activities in order to create impacts.[491]

It is critically important to distinguish the meaning of prevalence, as a measure of disease burden, and 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 this war against diabetes. 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 the prevalence, are other factors that should be considered before prevention programmes are judged as ineffective. Although surveys have been conducted on many millions of individuals across the globe, the data derived from these surveys has serious limitations. For example, of 200 countries analysed by NCD-RisC (NCD Risk Factor Collaboration),[4] 146 had population-based data that included direct measures of glycaemia, but only 108 countries had national data. The countries with the least data were located in central Africa, the Caribbean and Central Asia. Even when studies are available, they sometimes did not enrol younger adults or the elderly. Other limitations of the data include (increasingly) low response rates, especially in HICs, and the use of different definitions of diabetes (e.g., fasting plasma glucose, 75-gram OGTT, $HbA_{1c}$). As a result, it is difficult to compare prevalence between populations and track it over time, even within the same country. For studies using more than one of these measures, the difficulty is compounded by variations in how the measures are combined to define diabetes.

Until recently, the most common source of incidence data has been 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 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 an 'open cohort' design, in which new participants regularly enter the cohort. In practice, this rarely occurs, meaning that alternative sources are needed to determine secular trends.

### *11.1 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. In the earlier section, we have discussed about the use of EMR within the context of using data to identify gaps and improve care. In this section, we presented some of the opportunities in using data analytics for surveillance purposes. With increasing use of digital information, administrative databases are often populated with data from a number of sources, including dedicated disease registers, insurance claims and EMRs. Their strengths include their large size (typically more than 100,000 individual cases), the lack of susceptibility to volunteer bias or loss to follow-up, the capacity to produce year-on-year data at a relatively low cost, and the 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 research settings.

Indeed, unless the data are collected in a structured manner, there is uncertainty about how, and how well, diabetes has been diagnosed, and classified into types (e.g., T1D, T2D, diabetes in pregnancy). Since the overwhelming majority of adults with newly diagnosed diabetes have T2D, the total incidence remains a very good proxy for the incidence of T2D. On the other hand, changes in diagnostic criteria can have uncertain effects on observed incidence, depending on the rate at which the uptake of such changes has occurred. There is also no measure of undiagnosed diabetes and changes in screening behaviour can confound analysis of secular trends of incidence of clinically diagnosed diabetes. Analysis of secular trends in data sources that rely on the use of blood glucose lowering drugs to identify diabetes status can be confounded by changes in prescribing behaviour.

Despite these limitations, the feasibility of using population-based EMRs in measuring prevalence, incidence and secular trends has been demonstrated in some countries/areas with national or territory-wide database, with most of these countries/areas having universal health coverage. The design of these EMRs can serve as a reference for other clinical populations where similar data are not available due to resources or system factors. Panel 3 provides a list of clinical and laboratory measurement for collection at diagnosis and regular intervals (e.g., every 2-3 years) for clinical management and quality assurance purposes. By redesigning workflow and using a team approach to set up registers, we can fill some of these data gaps. By using a unique identifier, these databases can be linked to population statistics collected during census or other government departments such as socio-demographic[492] and meteorological data.[130]

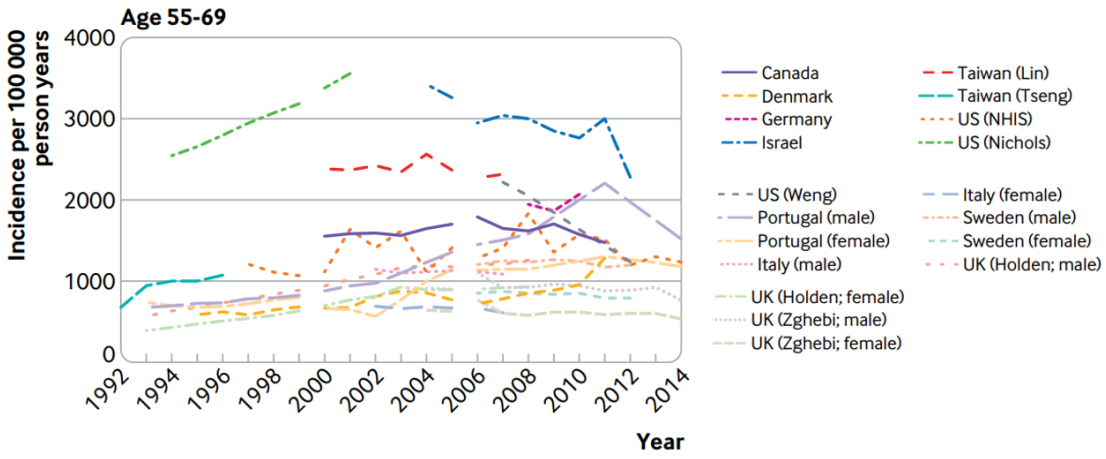
For accounting purposes, there is increasing digitalisation of hospitalisation records and disease registers (cancer, ischaemic heart disease, coronary interventions, heart failure, dialysis, depression).[493] In some countries where establishment of a national diabetes register is not practical, supporting a consortium of diabetes teams to collect data in a structured manner during their routine clinical practice may be an alternative. By combining structured databases with population statistics, EMRs and disease registers, we can identify upstream determinants, uncover treatment gaps, classify patient subgroups, perform analytics and evaluate the effectiveness of medications in real-world practice.[494] In some areas where large-scale RCT data are not available, these databases can be used to verify their effectiveness in real-world practice. For example, in Asia, these databases were used to confirm the benefits of statins in reducing cardiovascular events[495] including peripheral arterial disease[496] and CKD[497] to inform practice, albeit RCTs remain the gold standards. By sharing these best practices and real-world data, we can also perform comparative analysis on diabetes epidemiology and care standards in different populations and settings to advocate for better diabetes management and prevention.[439,498]

### *11.2 EMR and administrative databases suggest declining diabetes incidence in some countries*

Many of these EMRs and registers were established through introduction of quality improvement programmes where care organisation has resulted in structured collection of real-world data which has enabled the systematic analysis of clinical outcomes and effectiveness of interventions.[499] These data availability have also motivated decision-makers to invest in these programmes and increase their impacts.[498] In Israel, analysis of a large insurance group revealed an 18% decline in diabetes incidence during the period 2006–2012.[500] Analysis of claims data in the USA demonstrated a decline of incidence from 1.0% to 0.65% in 2007–2012.[501] Data from the Korean Health Insurance Database showed a decline in incidence in 2005–2009 and a consequent period of stabilisation until 2012.[502] In Hong Kong, while stabilising incidence trend in the middle-aged and falling trend in the elderly were observed between 2001 and 2016, there was significant increase in diabetes incidence in those under the age of 40.[50] Stabilisation of incidence has also been reported using data from a consortium of 11 integrated healthcare delivery systems with EMRs in 10 states of the USA in 2006–2011[503] and that of the Scottish National Register in 2004–2013.[504] In contrast, studies from England and Wales (1994–1998),[505] Portugal (1992–2015)[506] and Canada (1995–2007)[507] reported increases in diabetes incidence.

The first attempt to systematically collate published data on the trends of incidence of diabetes in adults (mainly due to T2D) revealed the majority of the studies came from administrative data sources rather than health surveys. While most studies reported increasing incidence between 1990 and 2005, from 2006–2014, 27% of reported populations had stable incidence over time, while 36% reported a declining trend; only 36% reported an increasing trend in the incidence of diabetes (Figure 20). The studies predominantly came from HICs, and trends may be different in LMICs. Furthermore, most studies could not determine the difference between a true fall in incidence and a change in diagnostic and screening behaviour.[508] Nevertheless, these encouraging trends are in contrast to the rising prevalence as reported as the main index in most analyses. With increasing popularity and adoption of EMRs and data digitalisation in high- and middle-income countries, many of which are undergoing major healthcare reforms, the use of administrative databases to define incidence and prevalence has become increasingly feasible.

**Figure 20. A systematic review showing the trends of annual incidence of diabetes during 1992-2014 among people aged 55-69. Most of the declining trends occur in high-income countries (HICs) with paucity of information in low- and middle-income countries. These data highlight the importance of societal determinants where key upstream factors notably, better education system, good governance and social policies in HICs may underline these favorable trends, calling for both population and individual-based strategies for prevention and control of diabetes and NCD (Magliano DJ et al, BMJ 2019).**




### *11.3 Use data analytics to practise precision medicine and discover new knowledge*

By creating these registers, EMR, population statistics, health surveys and cohort analysis, researchers can start to identify the linkage between causes, interventions and outcomes, based on which, algorithms and models can be developed for cross-validation as demonstrated in our case study using China as an example. These context-relevant models/algorithms can be used to prioritise interventions and identify patient subgroups who can be matched to different strategies, in order 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.[473]

## 12 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 RCTs. We have highlighted the utility of using structured data collection through quality improvement programmes to improve care standards and monitor clinical outcomes. Where such structured data are available, we were able to demonstrate the declining trends of incidence of diabetes and its complications in these populations. Through these databases, we also observed emerging trends and unmet needs in subpopulations. Apart from the multiple morbidities including frailty, depression and cognitive decline associated with ageing and long disease duration, the high event and death rates in YOD 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 healthcare barriers in many subpopulations, notably the migrant, minor ethnicity and underserved populations, in many HICs. Given the lifecourse 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. In order to implement what we have learnt and created to benefit those with or at risk of having diabetes and to make our healthcare sustainable, there is an urgent need to re-organise care by training non-physician personnel and use a team approach, assisted by ICT, to deliver data-driven integrated care to empower self-management and reduce multiple risk factors. To achieve this system change, alignment amongst payers, planners and providers are needed to address the pluralistic needs of patients. Meanwhile, additional research are needed to understand patient-important outcomes including values and preferences as well as psychosocial and cultural factors which influence lifestyle, self-management and health-seeking behaviours.

While globalisation has uplifted the living standards in many people living in LMICs, it has also dramatically changed the ecosystem and human behaviours, especially in many emerging economies. In these countries/areas hit hardest by the epidemic, the ill-prepared healthcare system, lack of capacity and insufficient data to guide actions have led to the majority of affected people not diagnosed, treated or controlled. Yet, examples from both HICs and LMICs have demonstrated that by implementing a society-community-individual strategy, we can potentially reduce the impacts of diabetes and other NCDs by creating a health-enabling environment and strengthening the healthcare 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 to many NCDs. This is a high calling which concerns all of us as global citizens who have contributed to this ecosystem, one way or another, to fuel the epidemic and as such, have the collective responsibilities to rise to this grand challenge to sustain our environment and use our finite resources wisely to preserve humanity.

## Author Contributions

**Co-conveners:** Juliana CN Chan (Chair), Edward W Gregg (Co-chair)
**Co-leads:** Epidemiology (Andrea OY Luk, Jonathan E Shaw), Prevention (Brian Oldenburg, Nicholas J Wareham), Treatment (Juliana CN Chan, Juan José Gagliardino), Type 1 diabetes (Graham D Ogle, Trevor J Orchard), Economics (Philip M Clarke, Ping Zhang)
**Members of Lancet Commission:** Carlos A Aguilar-Salinas, Peter H Bennett, Melanie J Davies, Björn Eliasson, Majid Ezzati, Rury R Holman, Alice PS Kong, Naomi S Levitt, Ronald CW Ma, Margaret McGill, Guang Ning, Ambady Ramachandran, Maria I Schmidt, Yutaka Seino, Wing-Yee So
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**Literature review:** Jean Adams, Nita G Forouhi, Xinyang Hua, Dianna J Magliano, Boon-Peng Ng, David Ogilvie, Jenna Panter, Meda Pavkov, Nigel Unwin, Martin White, Constance Wou

## Declaration of interest


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**Panel 1. Levels of care in type 1 diabetes in children and young adults, developed by the Life for a Child Programme.[392]**

| Tier | Level of priority | Insulin | Blood glucose monitoring | $HbA_{1c}$ | Complications screening | Diabetes education | Inter-clinic range of clinic mean A1c | Mortality and Complications |
|---|---|---|---|---|---|---|---|---|
| **Minimal care** | 1A | Human insulin, premixed insulin only, once to twice daily injections | Only at clinic | None | None/just weight | Minimal or no diabetes education. Care from general physician or paediatrician. | 12-14+% (108-130 mmol/mol) | High mortality from misdiagnosis and acute complications. Serious early-onset long-term complications very common in survivors. |
| | 1B | Human premixed insulin only, twice daily injections | 1-2 tests/day | Done in laboratory or 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% (80-108 mmol/mol) | Substantial mortality, serious early-onset long-term complications common. |
| | 1C | Human insulin, short- and long-acting, twice daily injections | | | | | 9-10.5% (75-91 mmol/mol) | |
| **Intermediate care** | 2A | Human insulin, multiple daily injections ("basal-bolus regimen") | 2-3 tests/day | 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, + dietitian and social worker if possible. Diabetes camps. Peer & school support, 24-hour emergency call service. | 8-9.5% (64-80 mmol/mol) | Infrequent mortality, serious long-term complications rare unless less-than-optimal blood glucose control. |
| | 2B | Human insulin, multiple daily injections +/- insulin pens | 4+ tests/day | | | | | |
| **Comprehensive care** | 3A | Insulin analogues ("basal-bolus regimen") with insulin pens | 5+ tests/day | Point-of-care | Full complications screening including all above + fundus photography, thyroid, coeliac (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 & school support, 24-hour emergency call service. | 6.5-8.5% (48-69 mmol/mol) | Mortality very rare, long-term complications long-delayed or prevented entirely except if blood glucose control is suboptimal. |
| | 3B | Insulin pump + consumables | | | | | | |
| | 3C | Insulin pump + consumables | Continuous glucose monitoring (CGM) + consumables | | | | | |
| | 3D | Artificial pancreas + consumables CGM + consumables | | | | | | |

**Panel 2. Delivery of a basic type 2 diabetes care plan using a nurse-healthcare 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.**

| Facilities, equipment and procedures | |
|---|---|
| No of patients | 800 patients depending on case mix |
| Workforce | 1 nurse and 1 healthcare assistant under medical supervision |
| Space | 200-300 square feet with basic office equipment (computer, email, telephone, fax, photocopying machines) for assessment and group education away from busy wards and clinics |
| Assessment tools | Monofilament and tuning fork (sensory neuropathy)<br>Hand-held ophthalmoscope or fundus camera (retinopathy)<br>Blood tests (plasma glucose, $HbA_{1c}$, lipids, renal/liver function, estimated glomerular filtration rate, uric acids, haematology)<br>Urine tests (urinary albumin:creatinine ratio) |
| Education tools | Charts and materials to explain nature of diabetes (causes/consequences), plan of follow-up (how often and by whom), self-monitoring (nature, how often) and treatment targets ($HbA_{1c}$, BP, LDL-cholesterol and body weight), syringes, insulin pens, monitoring devices for demonstration |
| Assessment items | Structured form for collection of age, sex, duration of diabetes, education, occupation, tobacco/alcohol intake, family history, self-care, feet (skin, nerves and blood vessels) and eye (visual acuity, cataract, retinopathy, history of laser or surgery), past history of medical illness (notably hospitalisations due to coronary heart disease, stroke, cancer, lower extremity amputation), major operations/procedures and significant symptoms (e.g., erectile dysfunction) |
| Computer database | Data collection for audit and recall purpose<br>Use risk equations to estimate future risk of events with simple to read report and decision support depending on availability and support |
| Frequency of assessment | Baseline assessment followed by 6–9 months with more frequent follow-up for education, reinforcement and treatment adjustment<br>Repeat assessment at 12 months to review progress and every 24–36 months with 4–6 monthly review once stable |
| Other activities | Group education, individual education, teaching of techniques, other classes on diet, physical activity, stress management, screening of family members and high-risk individuals (e.g., polycystic ovary syndrome, gestational diabetes, family members) and peer support depending on availability of resources |

| **Number of patients who can be served using a doctor-nurse-healthcare assistant team during a typical week** | | | | | |
|---|---|---|---|---|---|
| | Monday | Tuesday | Wednesday | Thursday | Friday |
| Morning session (4 hours) | | | | | |
| Structured assessment (~1 hour) and data entry | 3-4 patients | 3-4 patients | 3-4 patients | 3-4 patients | 3-4 patients |
| Afternoon session (4 hours) | | | | | |
| Group education by nurses (~45-mins) | 10 patients | | 10 patients | | 10 patients |
| Nurse/healthcare assistant support (manage register, phone counselling, patient reminder, urgent issues) | ✓ | ✓ | ✓ | ✓ | ✓ |

| **A flow chart showing the utilisation of person-hours to provide a structured, integrated assessment, education and supporting service over one year** | |
|---|---|
| Person-hours available | 8 working hours/day × 5 days/week × 48 weeks × 2 staff = 3,840 hours |
| Person-hours required | <u>Structured assessment at baseline and 1 year later (~1 hour each)</u><br>800 patients × 2 hours = 1,600 hours |
| Person-hours required | <u>Group education at baseline and 1 year later (~45-mins each)</u><br>800 patients × 1.5 hours = 1,200 hours |
| Person-hours remaining | <u>Provision of nurse/healthcare assistant support</u><br>1,040 hours |

**Panel 3. Recommended list of data for establishment of a diabetes register for risk stratification, clinical management and monitoring purpose. The fields highlighted in bold/italic represent a minimal dataset in less-resourced settings which should be documented at presentation and every 12-24 months, as appropriate. A validated risk stratification programme based on different combinations of these risk factors and complications was included as an example.**

| History taking | Clinical assessments | Laboratory tests |
|---|---|---|
| ***Year of assessment*** | ***Blood pressure*** | ***Fasting plasma glucose*** |
| ***Date of birth/age*** | Pulse rate | ***$HbA_{1c}$*** |
| ***Sex*** | ***Body weight*** | ***Total cholesterol*** |
| ***Year of diagnosis / diabetes duration*** | ***Body height*** | HDL-cholesterol |
| ***Types of diabetes*** | ***Waist circumference*** | LDL-cholesterol ***(or non-HDL-cholesterol)*** |
| ***Proneness to ketosis*** | ***Visual acuity*** | ***Triglyceride*** |
| Highest education attained | ***Retinopathy (non-proliferative, proliferative, sight-threatening if available)*** | ***Urinary albumin:creatinine ratio*** |
| ***Use of tobacco*** | ***Foot pulses*** | ***Plasma creatinine*** |
| Use of alcohol | Skin abnormalities | ***Estimated glomerular filtration rate (eGFR)*** |
| Family history of diabetes or maternal hyperglycaemia | Foot deformities | Blood haemoglobin |
| Family history of renal failure | ***Sensory neuropathy*** | |
| Family history of premature cardiovascular disease (<60 years) | | |
| Vaccination | | |
| Contraception | | |
| History of gestational diabetes | | |
| **Macrovascular complications** | **Microvascular complications** | **Comorbidities** |
| ***Ischaemic heart disease*** | ***Foot ulcers*** | ***Hyper/hypoglycaemic crisis*** |
| ***Heart failure*** | ***Laser or Eye surgery*** | Severe sepsis or chronic infections (e.g., tuberculosis, hepatitis B and C) |
| ***Stroke*** | ***Renal transplant*** | Any cancer |
| ***Non-traumatic lower extremity amputation (below/above knee)*** | ***Dialysis*** | Depression |
| **Oral glucose lowering drugs** | **Injectables** | **Cardiovascular drugs** |
| ***Metformin*** | ***Insulin*** (brand names, types, regimens and total daily dose) | ***HMG-CoA reductase inhibitors (statins)*** |
| ***Sulfonylurea*** | Insulin analogues (brand names) | ***Renin angiotensin system inhibitors*** |
| Alpha-glucosidase inhibitor | Glucagon-like peptide-1 receptor agonist (dose and regimen) | ***Aspirin*** |

| | | |
|---|---|---|
| | | ***Other BP lowering drugs*** |
| | | ***Other lipid regulating drugs*** |
| Thiazolidinediones | | Other antiplatelet drugs |
| Dipeptidyl peptidase-4 inhibitor | | |
| Sodium-glucose co-transporter 2 inhibitor | | |

**Risk stratification and follow-up actions (adapted from the JADE Programme)[464]**

| | Very High risk | High risk | Medium risk | Low risk |
|---|---|---|---|---|
| Cardiovascular disease and/or end-stage kidney disease | Yes | No | No | No |
| eGFR (ml/min/1.73m$^2$) | Severe (<15 or dialysis) | Moderate (15-60) | Mild (60-90) | Normal (≥90) |
| Other risk parameters | Not applicable | At least 3 | 2 | 0-1 |
| Risk scores for future events* | Very High | High | Moderate | Low |
| Estimated cumulative 5-year cardiovascular-renal event rates | 38% | 18% | 8% | 2% |
| Adjusted hazard ratio (referent group: 1) | 8.6 | 4.7 | 2.8 | 1 |
| Recommendations | 1. Structured comprehensive assessment by trained nurses and healthcare assistants at presentation to identify needs and build patient-provider relationships<br>2. Establish database to set up register and use data to stratify risk, individualise treatment targets and care plan<br>3. Use personalised data to provide feedback to patients and doctors with emphasis on risk profiles, attainment of treatment to multiple targets ($HbA_{1c}$, BP, LDL-cholesterol and body weight), use of statins and RASi and quit smoking<br>4. Use non-physician personnel to educate, empower and engage patients for self-management with social and peer support, as needed<br>5. Arrange early review by team members and adjust treatment strategies and provide support aiming to achieve control in 6–12 months<br>6. Arrange 3–6 monthly reviews by team members once stable<br>7. At least 6–12 monthly reviews even if low risk due to silent deterioration<br>8. Structured comprehensive assessment every 18–24 months for quality assurance especially if infrequent review | | | |
| Risk stratification parameters | 1. Current or ex-smoker<br>2. BMI ≥27.5 kg/m$^2$ or waist circumference ≥80 cm in women or ≥90 cm in men for Asians (ethnic-specific)<br>3. BP>130/80 mmHg or treatment with BP-lowering drugs<br>4. $HbA_{1c}$ >8% (64 mmol/mol)<br>5. LDL-cholesterol >2.5 mmol/L (100 mg/dL) and/or treatment with statins<br>6. TG >2.3 mmol/L (204 mg/dL) and/or HDL-cholesterol <1 mmol/L (39 mg/dL) and/or treatment with fibrates<br>7. Random spot urinary albumin:creatinine ratio >3.5 mg/mmol (women) or >2.5 mg/mmol (men)<br>8. Foot at risk with sensory neuropathy, skin changes (e.g., fungal infection, dry skin) and/or deformities (e.g., claw feet or hallux deformities)<br>9. Any retinopathy | | | |

Footnotes: *Once these registers are established, population-specific risk equations and models can be built to predict absolute event rates which can further improve the performance of the risk stratification programme.

**Table 1. Out-of-pocket (OOP) cost to people with diabetes in selected countries expressed in US dollar per person per year (refer to supplemental material for full reference list)**

| Diabetes type | | Annual total OOP cost per person for diabetes related care | | OOP as % of total diabetes related healthcare cost (%) | OOP as % of personal income or family income (%) | Sources |
|---|---|---|---|---|---|---|
| | | Original estimates, USD (year) | Converted to 2017 USD* | | | |
| **Low-income countries** | | | | | | |
| India | 1 | ~455 (2012) | ~521 | ~87 | ~16 | 1 |
| India | Not specified | ~515–525.5 (2009) | ~652–665 | 98–100 | NA | 2 |
| China | 2 | 596 (2013) | 666 | NA | 5.8 for the high-income household; 32.2 for the low-income household | 3 |
| Pakistan | 2 | ~197 (2006) | ~278 | ~100 | ~18 for the low-income household | 4 |
| Sudan | 1 | ~280 (2004) | ~429 | ~99 | ~23 | 5 |
| Nigeria | 2 | ~1,558 (2013)** | 1,742 | ~100 | NA | 6 |
| **High income countries** | | | | | | |
| USA | Not specified | Privately insured:~1,184 (2013) | ~1324 | Privately insured: ~11 | NA | 7 |
| | | Medicaid: ~260 (2008); Uninsured:~1,119 (2008) | Medicaid: ~339; Uninsured: 1,461 | Medicaid: ~2.7; Uninsured: ~40.4 | | 8 |
| | 1 | Medicare:~542 (2013) | ~606 | NA | NA | 9 |
| | 2 | Medicare:~529 (2013) | ~591 | NA | NA | 9 |
| Canada | 1 | ~808–3,693 (2015) | ~860–3,930 | ~22–81 | ~3–17 | 10 |
| | 2 | ~544–1,440 (2015) | ~579–1,532 | ~36–70 | ~2–9 | 10 |

Footnotes: *Adjusted to 2017 USD using the medical care part of consumer price index (https://www.bls.gov/cpi/data.htm)**. Recalculated by excluding non-medical cost such as transportation and diabetes diet from the original estimates. NA, not applicable.

**Table 2. Summary of evidence of modifiable risk factors and their associated risk of type 2 diabetes (refer to supplemental material for full reference list).**

| Modifiable risk factor category | Risk factor | References | Studies | Number of incident cases | Relative risk estimate |
|---|---|---|---|---|---|
| *Behavioural* | Overall physical activity | Smith et al, Diabetologia 2016[1] | 28 cohorts; 12 NA, 8 Europe, 6 Asia, 2 Australasia | 84,134 | RR 0.87 per 10 MET h/week difference in physical activity |
| | Sedentary behaviour | Wilmot et al, Diabetologia 2012[2] | 9 cohorts; 5 NA, 2 Europe, 2 Australasia | 23,230 | RR 2.12 comparing highest level of sedentary behaviour with least |
| | Fitness–enhancing physical activity | Zaccardi et al, Atherosclerosis 2015[3] | 7 cohorts; 4 NA, 2 Asia, 1 Europe | 8,564 | 0.95 per 1-MET higher baseline CRF |
| | Sleep | Shan et al, Diabetes Care 2015[4] | 10 cohorts; 5 NA, 2 Europe, 2 Asia, 1 Australasia | 18,443 | U-shaped relationship with lowest risk at sleep duration of 7–8 hours per day |
| | Dietary patterns (MD, DASH, AHEI) | Jannasch et al, J Nutr 2017[5] | 16 cohorts | Not specified | RR between extreme quantiles<br>MD 0.87<br>DASH 0.81<br>AHEI 0.79 |
| | Foods<br>Nuts/seeds<br>Whole grains<br>Red meat<br>Processed meat<br>Yoghurt<br>Sugar–sweetened beverages<br>Fibre<br>Glycaemic load | Micha et al, PLoS One 2017[6] | <br>5 cohorts<br>10 cohorts<br>9 cohorts<br>8 cohorts<br>9 cohorts<br>17 cohorts<br><br>5 cohorts<br>17 cohorts | <br>13,308<br>19,791<br>28,228<br>26,256<br>32,995<br>38,253<br><br>3,029<br>46,115 | <br>0.87 per 4s/wk<br>0.88 per 1s/d<br>1.19 per 1s/d<br>1.51 per 1s/d<br>0.82 per 1s/d<br>1.27 per 1s/d<br><br>0.76 per 30g/d<br>1.13 high vs. low<br>**s: serving* |
| | Macro–nutrients (e.g. saturated fat) | de Souza et al, BMJ 2015[7] | 8 cohorts; 4 Europe, 4 NA | 8,739 | Non-significant association RR 0.95 |
| | Micro–nutrients (e.g. vitamin D) | Song et al, Diabetes Care 2013[8] | 21 cohorts | 4,996 | RR high vs. low 0.62 |

| Modifiable risk factor category | Risk factor | References | Studies | Number of incident cases | Relative risk estimate |
|---|---|---|---|---|---|
| | Smoking | Pan et al, Lancet Diabetes Endocrinol 2015[9] | 88 cohorts | 295,446 | RR 1.37 current smokers vs. never-smokers |
| | Alcohol | Knott et al, Diabetes Care 2015[10] | 38 cohorts; 11 NA, 11 Europe, 12 Asia, 4 Australasia | 125,926 | RR 0.82 in those consuming 10–14 g per day vs. abstainers |
| *Social* | Work-related stress | Sui et al, PLoS One 2016[11] | 7 cohorts; 2 NA, 4 Europe, 1 Asia | 5,511 | Non-significant association RR 1.12 job strain vs. no job strain |
| | Depression | Knol et al, Diabetologia 2006[12] | 9 cohorts; 6 NA, 2 Europe, 1 Asia | Not specified | RR 1.37 depression vs. no depression |
| | Education | Agardh et al, Int J Epidemiol 2011[13] | 23 cohorts; 10 NA, 7 Europe, 2 Asia, 1 Middle East, 1 LA, 2 Africa | 21,978 | RR 1.41 high vs. low education |
| *Environmental* | Air pollution | Eze et al, Environ Health Perspect 2015[14] | 5 cohorts; 3 NA, 2 Europe | Not specified | RR 1.10 per 10 $\mu g/m^3$ $PM_{2.5}$ |
| | Food contaminants | Song et al, J Diabetes 2016[15] | 8 cohorts | Not specified | RR highest vs. lowest concentration: 1.91 dioxin, 2.39 total PCBs, 2.30 chlorinated pesticides |
| *Developmental* | Birth weight | Mi et al, Exp Ther Med 2017[16] | 8 cohorts; 3 NA, 4 Europe, 1 Asia | 3,892 | RR 1.55 low birth weight (<2500g) vs. normal |
| | Breast feeding | Horta et al, Acta Paediatr 2015[17] | 11 cohorts: Not specified | Not specified | RR 0.65 breast feeding vs. not |
| | Age at puberty | Janghorlani et al, Acta Diabetol 2014[18] | 10 studies; 3 Europe, 5 NA, 2 Asia | 22,085 | RR low age at menarche 1.22 vs. average age. |

Footnotes: AHEI, Alternative Healthy Eating Index; CRF, cardiorespiratory fitness; DASH, Dietary Approaches to Stop Hypertension; LA, Latin America; MD, Mediterranean diet; MET, metabolic equivalent of task; NA, North America; PCBs, polychlorinated biphenyls; $PM_{2.5}$, particulate matter ≤2.5μm in diameter; RR, relative risk.

**Table 3. A list of consensus recommendations by members of the Commission adapted from the 'best buys' of the World Health Organization (WHO),[327] United Nations Sustainable Development Goals[399] and WHO Convention Framework for Control of Tobacco[393] of potential interventions that could be employed as part of an integrated approach to type 2 diabetes prevention through government leadership, inter-sectoral collaborations and community mobilisation.**

| **Educational policies at all levels to improve literacy, self-management and lifelong coping skills** | | |
|---|---|---|
| **Environmental policies to build 'smoke-free' healthy cities with clean air, water and foods** | | |
| **Social policies to reduce poverty and inequalities and ensure care equity** | | |
| | **Diet** | **Physical activity** |
| **Supranational** | • International trade agreements on food and food-related commodities.<br>• International trade agreements on agriculture. | • International trade agreements on automotive industry.<br>• International agreements on climate change. |
| **National** | • Taxes on less healthy foods levied on producers or consumers; subsidies on healthier foods.<br>• Reformulation of commercially produced food to reduce density of less healthful nutrients.<br>• Restriction of marketing of less healthy foods on television and online.<br>• Mandatory food labelling of nutrients and calories on packaging and menus.<br>• Mandatory restriction of marketing of less healthy foods within stores (e.g., price promotions, placement, volume discounts).<br>• Industry-led reduction in portion size for packaged food and food served ready to eat. | • Taxes on transport mode (e.g., fuel duty).<br>• Subsidies to promote healthy travel (e.g., bike-to-work schemes and subsidised public transport). |
| **Regional** | • Regional school food policies (e.g., breakfast programmes, food and nutrition standards).<br>• Healthy food policies in other publicly-funded spaces (e.g., recreational settings, hospitals, government employers).<br>• Regional social marketing, mass media campaigns. | • School sports funding/organisation - school sports partnerships.<br>• Regional taxes or subsidies on transport mode.<br>• Regional social marketing, mass media campaigns. |

| Educational policies at all levels to improve literacy, self-management and lifelong coping skills | | |
|---|---|---|
| **Environmental policies to build 'smoke-free' healthy cities with clean air, water and foods** | | |
| **Social policies to reduce poverty and inequalities and ensure care equity** | | |
| | **Diet** | **Physical activity** |
| **Local** | • Local restrictions of marketing of less healthy foods in schools, outdoors and in recreational settings.<br>• Use of planning system to regulate food outlets selling/serving food of differential healthfulness. | • Promotion of walking and cycling infrastructure.<br>• Development of local space for physical activity (e.g., parks, leisure centres, playing fields).<br>• Use of local planning regulation to promote walkable neighbourhoods.<br>• Use of local fiscal levers to promote healthy travel (e.g., subsidised public transport, parking charges and congestion charging).<br>• School-based physical activity promotion programmes. |
| **Community** | • Faith-based organisations cooking/food interventions. | • Faith-based organisations physical activity interventions. |
| **Individual** | • Individual, group or digital dietary interventions. | • Individual, group or digital physical activity interventions. |

**Table 4. Major randomised primary prevention studies in type 2 diabetes (refer to supplemental text for full reference list).**

| Study (Year) | Country | Number of participants | Intervention | Duration of follow-up | Relative risk reduction (%) |
|---|---|---|---|---|---|
| Da Qing Diabetes Prevention Study (1997) CDQDPS[1] | China | 577 | Lifestyle modification | 6 years | Diet: 31.0 Exercise: 46.0 Diet-plus-exercise (D+E): 42.0 |
| Da Qing Diabetes Prevention Extended Study (2008) CDQDPS[2] | | | | 20 years | 43.0 (D+E) |
| Da Qing Diabetes Prevention Extended Study (2014) CDQDPS[3] | | | | 23 years | 45.0 (D+E) |
| Diabetes Prevention Study (2001)[4] | Finland | 522 | Lifestyle modification | 3.2 years | 58.0 |
| Diabetes Prevention Extended Study (2013)[5] | | | | 13 years | 38.0 |
| Diabetes Prevention Program (2002)[6] | USA | 3,234 | Lifestyle modification, Metformin | 2.8 years | Lifestyle 58.0; Metformin 31.0 |
| Diabetes Prevention Program Outcome Study (2009)[7] | | | | 10 years | Lifestyle 34.0; Metformin 18.0 |
| Diabetes Prevention Program Outcome Study (2015)[8] | | | | 15 years | Lifestyle 27.0; Metformin 18.0 |
| Prevention of type 2 diabetes by lifestyle intervention (2005)[9] | Japan | 458 | Lifestyle modification | 4 years | 67.4 |
| Indian Diabetes Prevention Programme-1 (2006)[10] | India | 531 | Lifestyle modification; Metformin | 2.5 years | Lifestyle 28.5 Metformin 26.4 |
| Indian Diabetes Prevention Programme-2 (2009)[11] | India | 407 | Lifestyle modification plus Pioglitazone | 3 years | No benefit by adding pioglitazone |
| Zensharen Study for Prevention of Lifestyle Diseases (2011)[12] | Japan | 641 | Lifestyle modification | 3 years | 44.0 |
| Indian SMS Study (2013)[13] | India | 537 | Lifestyle modification | 2 years | 36.0 |

| Study (Year) | Country | Number of participants | Intervention | Duration of follow-up | Relative risk reduction (%) |
|---|---|---|---|---|---|
| Diabetes Community Lifestyle Improvement Programme (2016) (D-CLIP)[14] | India | 578 | Lifestyle modification plus stepwise addition of metformin (for those at highest risk of conversion to diabetes) | 3 years | 32.0 |

**Table 5. Demographic and organisational factors that influence type 2 diabetes prevention policies with contrast between Jamaica[407] and England[509]**

| | Country | | |
|---|---|---|---|
| | | **Jamaica** | **England** |
| Country demographics and healthcare | Total adult population (1000s) | 2,881 | 65,640 |
| | GDP per capital, purchasing power parity (current international dollar) | 8,835 | 42,609 |
| | Total healthcare expenditure (THE) of GDP (%) per capita (USD) | 5.4/266 | 9.1/3,935 |
| | General government health expenditure (% of total health expenditure) | 52 | 83 |
| | Density of physicians (total number per 1,000 population) | 0.4 | 2.8 |
| | Density of nursing and midwifery personnel (total number per 1,000 population) | 1.1 | 8.4 |
| Current burden of disease | Prevalence of diabetes in women/men (%) | 14.4 (7.8–23.3)/ 9.3 (4.5–16.0) | 4.9 (3.1–7.4)/ 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 2025 in women/men (%) | 21.6 (7.2–49.8)/ 13.7 (3.7–33.8) | 5.4 (2.1–11.6)/ 7.8 (3.1–15.9) |
| Current prevalence of risk factors | Prevalence of high blood pressure in women/men (%) | 19.2 (12.0–27.7)/ 24.5 (15.6–34.8) | 12.4 (9.0–16.1)/ 17.9 (13.0–23.2) |
| | Prevalence of overweight and obese in women/men (%) | 63.4 (56.5–70.0)/ 48.3 (41.0–55.4) | 58.5 (53.8–63.0)/ 67.7 (63.3–72.0) |
| | Prevalence of obesity in women/men (%) | 33.0 (25.7–40.0) / 15.19 (10.0–21.2) | 28.3 (24.2–32.5)/ 26.2 (22.1–30.5) |
| Future prevalence of risk factors | Estimated prevalence of obesity in 2025 in women/men (%) | 43.2 (29.5–59.1) / 25.7 (13.2–43.6) | 37.6 (28.7–47.7)/ 37.8 (27.7–49.9) |
| Quality of diabetic care | People with diabetes with $HbA_{1c}$/ fasting blood glucose within target range (%) | 43 | 65.7 |
| | People with diabetes with lipids under control | No population based data | 77.1 |
| | People with diabetes with BP <140/90 mmHg (%) | 16 – 94 % | 73.6 |
| | Diabetes register | Yes | Yes |
| 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 |
| | Insulin available in the public sector | Yes | Yes |

| | Country | | |
|---|---|---|---|
| | | **Jamaica** | **England** |
| Current available treatments | Metformin available in the public sector | Yes | Yes |
| | Statin available in 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 | 2016 first wave of NHS Diabetes Prevention Programme covering 26 million people |

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# Use Data To Transform Diabetes Care And Lives With Diabetes
# The Lancet Commission on Diabetes

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## Executive Summary

2020 will go down in history as the year when the global community is awakened to the fragility of human health and the inter-dependence of ecosystem, economy and humanity. In the midst of the pandemic of coronavirus disease (COVID)-19, the vulnerability of people with diabetes during emergencies became fully evident by their 3–5 fold increased risk of severe disease including death, especially in those with poorly controlled diabetes and/or comorbidities versus those without diabetes, with consequential heavy tolls on healthcare systems and the global economy.

In this Lancet Commission on Diabetes which embodies four years of extensive work on data curation, synthesis and modelling, we urge policymakers, payers and planners to collectively change the ecosystem, build capacity and improve practice environment to enable practitioners to systematically collect data during routine practice and use the data more 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 (NCDs). The emerging evidence regarding the possible damaging effects of coronavirus on beta-cells implies possible worsening of these two pandemics of diabetes and COVID-19 infection, adding to the urgency of these collective actions.

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

Globally, in 2019, 463 million people had diabetes with 80% coming from low- and middle-income countries (LMICs). Over 70% of global deaths are due to NCDs including diabetes, cardiovascular disease (CVD), cancer and respiratory disease. On average, diabetes reduces life expectancy in middle-aged people by a mean of 4–10 years and independently increases the risk of CVD, renal and cancer deaths by 1.3–3.0 fold. It is amongst 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 epidemic, we explain how the concept of environment-agent-host interactions, often used to explain marked variations in risk exposure and outcomes in communicable disease, also applied to diabetes where ecosystem and human behaviours are key upstream factors. In this light, we highlight the impacts of maternal hyperglycaemia on adolescent obesity and the emerging epidemic of young-onset diabetes (YOD) with multiple aetiologies, and their high risk of premature death and complications. Apart from ageing, environmental and socioeconomic factors, notable underlying risk associations of diabetes especially in underserved communities are poor nutrition, physical inactivity, depression, poverty and low levels of education. The multidimensional nature of these risk factors calls for a wide-ranging society-community-individual strategy to integrate prevention, diagnosis and care of type 2 diabetes (T2D).

Despite the availability of efficacious medications proven to reduce cardiovascular-renal events and death rates in clinical trial settings, their lack of provision and access to trained healthcare providers (HCPs) 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 more systematic approach to stratify risk, classify disease subtypes, identify specific needs and personalise care. With regards to type 1 diabetes (TID), we present the continuing high standardised mortality ratios (SMRs), especially in those living in deprived communities and LMICs. Poor access to life-saving technologies, including insulin and blood glucose monitoring tools, as well as inadequate education for self-management have resulted in many avoidable deaths and acute emergencies in these young patients.

Based on best evidence and best practices, we summarise the benefits of more effective management of multiple risk factors among patients with diagnosed diabetes where 1) sustained weight reduction in obese patients by 15 kg or more can induce remission in T2D for up to 2 years; 2) reducing glycated haemoglobin ($HbA_{1c}$) by 0.9% (10 mmol/mol), systolic blood pressure (BP) by 10 mmHg and/or low-density lipoprotein cholesterol (LDL-cholesterol) by 1 mmol/L (39 mg/dL) can each independently reduce the risk of CVD and/or all-cause death by 10–20% in T2D; 3) reducing multiple risk factors including the use of statins and renin-angiotensin system inhibitors (RASi) can prevent cardiovascular-renal events by 20–40% in individuals with or at risk of having diabetes; 4) using sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1-RA) can reduce cardiovascular-renal events and death rates by up to 40% independent of their blood glucose lowering effect; 5) using data-driven, team-based integrated care by re-organising health care provision can reduce CVD and all-cause death in T2D by 20–60%; and 6) implementing structured lifestyle intervention and metformin use can each prevent or delay T2D in individuals with impaired glucose tolerance by 30–50%.

In order to translate these evidence-based risk reduction strategies, we put together an implementation plan showing how by training non-physician personnel to form a diabetes team, we can re-design workflow and use information and communication technology (ICT) to set up diabetes registers and use the data collected to empower self-management, improve provider-patient communication and reduce multiple risk factors. Using this multicomponent strategy, we can identify high-risk patients with T1D, YOD, and those with comorbidities, atypical diabetes and complex needs who require inter-disciplinary management with ongoing support. By using prospectively designed and unified data-management systems, we can support the collective needs of clinical, surveillance and research activities related to diabetes and create societal impacts by transforming care and informing policies.

Using modelling, we have estimated the impacts of our proposed 'integrated actions' versus the current 'fragmented actions'. In high-income countries (HICs), the SMR for patients with T1D is 2.5 compared to that of 4.9–33.9 in LMICs. In 2017, 1.1 million young patients had T1D diagnosed under the age of 20 years and an estimated 14,466 aged less than 25 years died. If all patients with T1D were to receive guideline-based comprehensive care with access to intensive insulin therapy, personalised education and regular complications assessments, we estimate that 12,092 of these deaths could have been averted. For T2D, in 2017, 217 million affected individuals (age 30–69 years) lived in 10 LMICs and 3.2 million are estimated to have died after 3 years with 1.3 million of these deaths due to CVD. By ensuring access to essential medications and improving control of BP, $HbA_{1c}$ and LDL-cholesterol in 70% of diagnosed patients, we estimate 0.8 million of these premature deaths might have been prevented.

If a society-community-individual strategy aimed at reducing illiteracy and social disparity as well as creating a health-enabling environment supported by a community-based health-promoting policy linked to an integrated care system were to be implemented, for a population of 1 million in China, we could potentially avert the occurrence of 11,065 cases of diabetes and 6617 CVD events in the next 5 years, which would increase to 33,773 and 51,863, respectively, after 20 years. These figures would translate to 44 million fewer cases of diabetes and 67 million fewer CVD events in the 1.3 billion Chinese population.

**Key messages**

1. The ensured access to insulin, patient education and blood glucose monitoring tools can prevent premature deaths and emergencies in young patients with T1D especially in disadvantaged communities.
2. The impact of maternal hyperglycaemia on childhood obesity requires a multicomponent lifecourse strategy to prevent YOD which may benefit our next generation.
3. The complex aetiologies, notably psychosocial needs especially in YOD, call for structured assessment in order to personalise care for reducing premature NCD and death.

4. The diverse environmental, behavioural, and socioeconomic causes of T2D require a multitiered societal and population-based prevention strategy.
5. The marked differences in diabetes diagnosis, treatment and outcomes between LMICs and HICs are likely due to differences in investment, capacity, healthcare systems and care organisation.
6. The sustained reduction of common cardiometabolic risk factors including smoking cessation, and use of statins, RASi, SGLT2i and GLP1-RA therapies can reduce cardiovascular-renal diseases and all-cause death in patients with T2D.
7. The delivery of team-based care can enable systematic collection of data during routine clinical practice to improve the quality of electronic medical records (EMR) and establish registers for surveillance, prevention and treatment.
8. The strengthening of existing infrastructures for providing long-term care and creating career paths for physicians with knowledge and skills to re-organise diabetes care, train non-physician personnel and use technology effectively can improve the accessibility, sustainability and affordability of diabetes prevention and care.

**Recommendations**

We recommend the establishment of a Global Diabetes and NCD Task Force, led by policymakers, consisting of stakeholders across different sectors, including but are not limited to, healthcare institutions, academia, school, industry, professional bodies/experts, nongovernment organisations to design, steer and support a multicomponent strategy to address the multidimensional nature of diabetes and other NCDs, in line with the United Nations Sustainable Developmental Goals, World Health Organization (WHO) NCD Global Monitoring Framework, WHO Convention Framework for Tobacco Control and professional practice guidelines, aimed at:

1. Closing the diabetes prevention gap

   We recommend policymakers, planners and managers to implement context-relevant policies through inter-sectoral, inter-department and inter-disciplinary collaborations aimed at:

   - strengthening the educational, environmental, 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 the use of non-physician personnel, assisted by ICT, to implement lifestyle intervention programmes and reduce the risk of T2D in high-risk individuals with linkage to a prepared healthcare system for managing people detected with undiagnosed diabetes and those who have been diagnosed
   - aligning the expectation of care providers, industry and payers to ensure access, affordability and sustainability of the continuing care of people with or at risk of diabetes

2. Closing the diabetes professional knowledge gap

   We recommend universities, accreditation bodies and professional organisations to train knowledge workers as well as funding agencies to support research programmes in the field of diabetes especially in LMICs aimed at:

   - re-designing the curriculum for undergraduates of social, health and medical disciplines to better enable the workforce to provide the acute and long-term healthcare needs of people with or at risk of diabetes and other NCDs
   - 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 healthcare discipline essential for maintaining care standards, translating evidence to practice and providing on-job training
   - promoting research programmes focusing on design, implementation and evaluation of delivery of diabetes care and prevention programmes in a naturalistic environment

3. Closing the diabetes care gap

   We recommend policymakers, payers and planners to increase investments in diabetes care, focusing on prevention of complications, by strengthening the healthcare system aimed at:

- establishing hospital and community-based diabetes centres and teams including professional and non-physician personnel (e.g., trained community health workers/peers) to provide continuing care to people with or at risk of developing diabetes
- ensuring that all individuals with T1D are registered with access to insulin, equipment for self-monitoring of blood glucose and appropriate health education to promote self-management
- re-designing workflow and using 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 (e.g., control of cardiometabolic risk factors, renal function, use of organ protective drugs and self-management) for quality assurance
- leveraging existing facilities and workforce and providing career advancement for HCPs specialised in diabetes to scale up the delivery of data-driven, team-based integrated care

4. Closing the diabetes data gap
   We recommend public health workers, HCPs and researchers, with administrative support, to work collaboratively and use registers, administrative data and audits to complement randomised clinical trials for informing decision-making at patient, providers and system levels by:
   - integrating and analysing these databases to facilitate the monitoring of prevalence (disease burden) and incidence (effects of intervention)
   - using this real-world evidence to evaluate the effectiveness of new interventions and technologies as well as developing more sophisticated outcome models to project their cost-effectiveness in different subpopulations in naturalistic environments to better inform decision-making
   - detecting the population trends of diabetes and its complications and emerging unmet needs to guide practice and policies

# 1 Introduction

***By implementing what we have learnt 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***

According to the World Health Organization (WHO), diabetes is diagnosed either by a fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during a 75-gram oral glucose tolerance test (OGTT) and/or glycated haemoglobin ($HbA_{1c}$) ≥6.5% (48 mmol/mol). It is a heterogeneous condition with complex aetiologies, including but not limited to, environmental, lifestyle and genetic factors. The great majority (95%) of affected individuals have type 2 diabetes (T2D), characterised by various combinations of insulin resistance and insulin deficiency. In this document, the term 'diabetes' refers to chronic hyperglycaemia fulfilling these criteria irrespective of the aetiologies, unless otherwise stated.

In the last several decades, the scientific community has amassed a large body of knowledge about the growing health and socioeconomic burden of T2D and its multidimensional nature. There is now strong evidence indicating that T2D is preventable and may 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 declining, although there remain major gaps in care, data and outcomes especially in low- and middle-income countries (LMICs). In these countries, insufficient infrastructure and capacity, high costs of medications, fragmentation of healthcare systems, health illiteracy and social disparity are major barriers, resulting in many individuals with type 1 (T1D) or T2D not being diagnosed, treated or managed. Despite increasing healthcare 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 where ageing, poor nutrition and physical inactivity are major drivers. In LMICs, other factors such as environmental pollution, food insecurity and social disparity may also contribute. Once diabetes develops and if not adequately managed, its lifelong nature can have enormous impacts on the individuals, families and society. Given the WHO definition of health as 'a state of physical, mental and social wellness', diabetes is a prime example of how societal factors become major players in disease development which in turn can affect the individuals, families and society.

### *1.1 The Lancet Commission on Diabetes*

In 2016, 26 experts in public health, clinical care, epidemiology and health economics were brought together by The Lancet to 1) review the evidence and knowledge gaps in the field of diabetes, 2) develop strategic and actionable plans ('actions') and 3) estimate the impacts of 'no action' versus 'actions' with a focus on LMICs. In this evidence-based document, 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, which contribute to the lack of provision or poor access to quality preventive care. The consequences are escalating and unsustainable healthcare costs due to complications, which are often preventable in the first place, not only in LMICs but also HICs.

To address these challenges, we have provided a framework where, by redesigning care settings, workflow and team structure, we can implement an integrated diabetes detection, prevention and management plan to reduce incidence of diabetes-related complications and T2D in high-risk individuals. These measures must be supported by inter-sectoral policies in order to mitigate the negative impacts of societal determinants and create long-term benefits. Using epidemiological, clinical trial and real-world data, we have modelled the short- (1–3 year), mid- (10 years) and long-term (20 years) impacts of implementing a multicomponent strategy including societal measures aimed at reducing the burden of diabetes and non–communicable disease (NCD), which will save millions of deaths and billions of dollars in LMICs.

This report provides a data-driven argument for the public, patients, practitioners, payers and policymakers that despite the daunting nature of diabetes and NCD, there are numerous solutions to avert the grave consequences of this global epidemic of diabetes. They will require a collective transformation of our ecosystem and healthcare environment in pursuit of adherence to evidence-based professional guidelines, the WHO NCD Global Monitoring Framework, WHO Convention Framework for Tobacco Control, and United Nations Sustainable Developmental Goals for our society, community and humanity.

## 2 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 (CVD, including mainly ischaemic heart disease and stroke), cancer and respiratory disease, with diabetes increasing the risk of CVD, renal and cancer-related deaths by 1.3–3.0 fold.[1] In 2019, 463 million individuals were affected by diabetes.[2,3] In a worldwide trend analysis, the prevalence of diabetes has doubled in men and increased by 60% in women over the past 25 years.[4] Estimates from the United States of America (USA) and Australia indicate that diabetes reduces life expectancy by at least 6 years when diagnosed at the age of 40 and at least 4 years when diagnosed at the age of 60,[5-7] with childhood-onset T1D having an even greater impact in the absence of adequate care.[8] A 50-year old man in China diagnosed with diabetes at the age of 50 in year 2000 lost on average 9 years of life compared with his peers without diabetes.[9]

According to the WHO, one-third of all global deaths are due to CVD including stroke and ischaemic heart disease. Diabetes confers a 2.3–fold increased risk of CVD[10] while 30% of individuals with

diabetes die from CVD.[11] In less-resourced areas, acute medical crisis such as diabetic ketoacidosis or hyperglycaemic hyperosmolar states remain 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 United Kingdom (UK).[9,12,13] During the recent coronavirus disease (COVID-19) pandemic, patients with diabetes had a 2–5 fold increased risk of severe disease including death compared to those without diabetes, especially amongst those with poor glycaemic control, multiple risk factors or diabetes-related complications.[14,15] Despite the silent nature of diabetes, the COVD-19 global emergency has exposed the vulnerability of these individuals with heavy tolls on healthcare systems, economies and humanity.[16]

### *2.1 Cardiovascular, renal and cancer deaths*

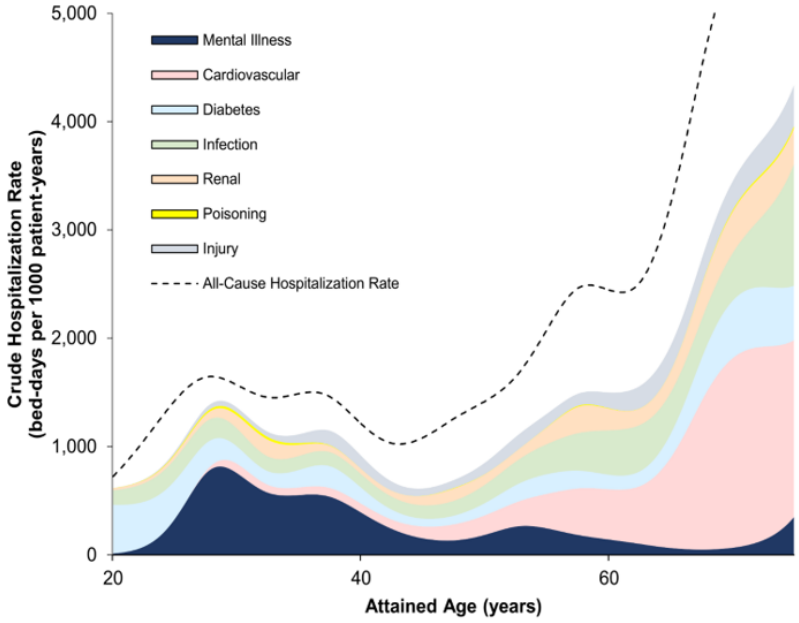
In the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, after accounting for multicausality, 63% of 10.8 (95% confidence interval (CI): 10.1–11.5) million deaths from cardiovascular-renal diseases in 2010 were attributable to the combined effect of high blood pressure (BP), blood glucose, serum cholesterol and body mass index (BMI), compared with 67% [7.1 (6.6–7.6) million] of similar deaths in 1980.[17] In the Global Burden of Diseases, Injuries and Risk Factors Study (GBD 2017), smoking, high systolic BP, high plasma glucose, alcohol use and history of preterm birth in men and, high systolic BP, high plasma glucose and high BMI in women were the leading risk factors in terms of attributable disability-adjusted life years (DALYs).[18] In the USA, the incidence of diabetes-related complications has fallen during the past two decades, but the rate of decline has been much slower for end-stage kidney disease (ESKD) than for CVD.[19] In the US Renal Register, the percentage of ESKD due to diabetes has risen steadily and is presently at around 50%.[20] This rising trend may be due to improved survival from cardiovascular insults in individuals with diabetes, which has given kidney disease more opportunities to evolve.[21]

The high incidence of cancer as a cause of death in people with diabetes was recognised as far back as 1914.[22] With ageing and better prevention of and survival from CVD, there is an increase in this double burden of diabetes and cancer. Even after adjustment for shared risk factors such as age, obesity and smoking, diabetes increases the relative risk for all-site cancer (except for prostate cancer) by 1.2–2.0 fold, as compared with the general population.[1,23] While the mechanisms underlying the close association between diabetes and cancer need further elucidation, the increased risk of cancer in T1D[24] and the independent associations between blood glucose and cancer risk[25] support an important role of dysregulation of glucose metabolism in this risk association. In a recent 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.[26]

### *2.2 Diabetic foot and eye complications*

In a systematic review of 35 population-based studies, with diabetic retinopathy (DR) ascertained from retinal photographs, the overall prevalence was 34.6% for any DR, 7.0% for proliferative DR, 6.8% for 'diabetic macular oedema' and 10.2% for vision-threatening DR.[27] These figures implied an estimated global burden of 93 million individuals with DR and 28 million individuals with sight-threatening stages of DR in 2010.[27] In another systematic review of 8 prospective population-based studies on DR, the annual incidence of DR was 2.2–12.7% with an annual progression of 3.4–12.3%, without sex differences. Although hypertension was not reported as a significant risk factor, suboptimal glycaemic control increased the risk of DR by 10–40%.[28] Individuals with diabetes are 7–30 times more likely to have non-traumatic lower extremity amputations than the general population, accounting for over half of all such amputations.[29,30] Good podiatry care often prevents limb amputation and people who need amputation usually have disseminated vascular disease which contributes to their poor survival rate. In HICs such as North America, Europe and Australia, the incidence of lower extremity amputation among individuals with diabetes has fallen over the past decade.[19,29] The updated estimates of incidence of lower extremity amputation ranged between 1.9 and 3.9 per 1000-person-years in Europe and the USA.[30-32] However, the latest analysis of the national data in USA suggests resurgence of non-traumatic lower extremity amputation in the younger to middle-aged population in recent years.[33]

**Figure 1. Crude hospitalisation rates (bed-days per 1000 patient-years) for selected principal diagnoses, by attained age, among persons with young-onset type 2 diabetes in the Hong Kong Diabetes Register showing the excess burden of hospitalisation and mental illness (Ke C et al Ann Int Med 2019).**




### *2.3 Diabetes, comorbidities and mental health – impact on patients and caregivers*

Individuals with diabetes are twice as likely to suffer from depression than is the general population, a condition often under-recognised and untreated.[34,35] Similarly, individuals with depression are more likely to develop diabetes.[36] Apart from environmental stressors (e.g., socioeconomic deprivation and life events), diabetes and depression may share common behavioural risk factors (e.g., 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.[37] A diagnosis of diabetes calls for changes in lifestyle, long-term use of medications, regular visits to healthcare providers (HCPs) and so on. These demands on day-to-day living may contribute to the high prevalence of anxiety, stress and/or depression, affecting one in 3–5 individuals with T2D.[36] These negative emotions can set up a self-perpetuating cycle of suboptimal self-care and treatment non-adherence, frequent hypo- and hyperglycaemic episodes and poor clinical outcomes.[38,39]

In a recent report using both registers and population-based electronic medical records (EMR) that included 0.42 million Chinese adults with incident T2D observed between 2002 and 2014, data modelling indicated that patients with young-onset T2D (YOD), diagnosed before the age of 40, spent an average of 100 hospital-days from diagnosis to age of 75 with one-third of the hospitalisations due to mental illness before the age of 40 (Figure 1).[40] The frequent clustering of multiple morbidities increases the complexity of the management of T2D. In the UK, using the Clinical Practice Research Datalink, researchers analysed the co-occurrence of 18 chronic conditions, including diabetes, and reported that compared with those living in affluent areas, patients living in the most deprived areas had more comorbidities which frequently clustered with depression especially in women.[41] Using data on demographics, comorbidities and disease duration in patients with T2D, researchers from Singapore reported 5 clusters where clustering of depression in young women with short to moderate disease duration as well as in older patients with moderate to long disease duration and multiple morbidities were the highest tertiary health care users.[42]

Adding to this challenge is the growing burden of diabetes, cognitive decline and dementia.[43] The presence of these comorbidities does not only affect the quality of life of the patients but also markedly increases the emotional burden on the caregivers, which is amplified by poor access and continuity of care and insufficient communication amongst different service providers and specialities. While there are examples of good practice often due to the behaviour of individual physicians, a system-wide approach requiring better communication and care coordination is needed to address the physical and emotional needs of both the patients and their caregivers.[44]

## 3 YOD requires better risk stratification and disease classification

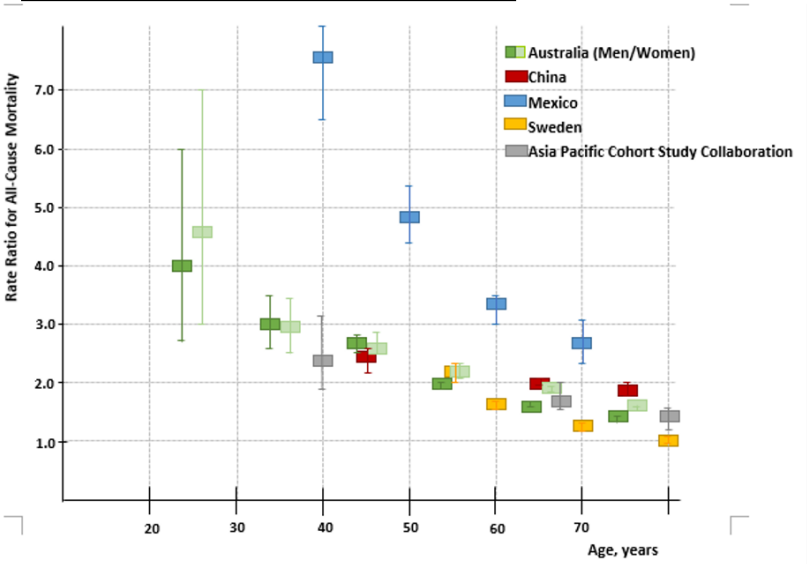
From 1980 to 2014, the global age-standardised diabetes prevalence in adults aged 20 years and older increased from 4.3% (2.4–7.0) to 9.0% (7.2–11.1) in men, and from 5.0% (2.9–7.9) to 7.9% (6.4–9.7) in women. These trends were driven largely by ageing and worsening risk factors, notably obesity, as well as by declining death rates among individuals with diabetes in some countries. During the same period, the age-standardised prevalence in working age (20–64 years) adults 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.[4] In some communities (e.g., Native Americans), there was a rise in total diabetes prevalence in children and adolescents which was mostly attributed to T2D.[45]

### *3.1 YOD increases risk of premature death, morbidities and hospitalisations*

In the early 1970s, Pima Indians diagnosed with T2D before the age of 25 were reported to have high rates of morbidities (ESKD, amputation, blindness) and death after an average of 15–20 years duration of diabetes.[46,47] Similar findings were also reported in Japanese patients with YOD with higher rates of diabetic nephropathy compared with T1D.[48,49] In Hong Kong, the rising incidence of both T1D and T2D in people under the age of 40[50] concurred with the most rapid rate of increase in renal replacement therapy in the 45–65 age group.[51] In the clinic-based Joint Asia Diabetes Evaluation (JADE) Register, 1 in 5 adults with diabetes in Asia had YOD.[52] In a survey of 0.42 million Chinese adults with diabetes under public care, patients with YOD had the highest hospitalisation rates by 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 CVD and 1.7 for infection, compared with their late-onset counterparts.[40]

The high prevalence of complications in YOD is driven mainly by long disease duration.[53] Compared with age-matched individuals without diabetes, the mortality rate ratios are consistently higher in younger age groups, in part due to their low background mortality (Figure 2).[9,12,54] In the USA, a temporal decline in the rates of CVD and related death among older individuals was far less evident in their younger counterparts.[19] In the Swedish National Diabetes Register, patients with T2D diagnosed before the age of 40 had 2–4 fold higher risk of cardiovascular and non-cardiovascular mortality, heart failure and ischaemic heart disease compared with control populations. All these risks were attenuated progressively with increasing age and substantially in those diagnosed after the age of 80.[55] Using data from the National Diabetes Services Scheme between 1997 and 2011 involving 743,709 Australians with T2D, a 10-year earlier diagnosis (equivalent to 10 years' longer duration of diabetes) was associated with a 20–30% increased risk of all-cause death and about a 60% increased risk of death due to CVD.[56] In the Hong King Diabetes Surveillance Database including 770,778 patients with T2D, all-cause and cause-specific death rates had declined by 50–80% between 2001 and 2016. However, in the 20–44 age group, the death rates did not decline with the standard mortality ratio (SMR) fluctuating between 4.92 and 7.89 during the same period.[57]

**Figure 2. Standardised rate ratio (SRR) for all-cause mortality for people with diabetes compared to the general population, according to age and countries (refer to supplemental text for details of references).**




### *3.2 Diagnosing, classifying and managing YOD and other diabetes subtypes*

In the early 1980s, amongst Caucasians, over 90% of patients with diabetes diagnosed young (e.g. before the age of 40) were considered to have classical T1D due to autoimmune islet destruction with acute ketosis and absolute insulin deficiency.[58] In HICs, the tendency to develop ketosis means that patients with T1D are less likely to default the medical system for too long before they present with acute emergencies.[59] However, in non-Caucasian populations including those from Mexico,[60] India[61] and China,[62] classical, ketosis-prone T1D remains relatively uncommon in young adults diagnosed with diabetes. In Chinese patients with YOD, only 10% had classical T1D. In the remaining patients, 60% were overweight and 30% were normal-weight. After 9 years of follow up, overweight patients with YOD had a hazard ratio of 15.3 (2.1-112.4) for CVD and of 5.4 (1.8-15.9) for ESKD while patients with T1D had the lowest event rates.

In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study and the SEARCH for Diabetes in Youth Study in the USA, adolescent-onset T2D is characterised by rapid deterioration in beta-cell function and poor metabolic milieu versus T1D or late-onset T2D.[63] In the TODAY Study, 50% of patients with youth-onset diabetes (10-17 years) treated with metformin monotherapy had treatment failure ($HbA_{1c}$>7.9% [63 mmol/mol] for at least 6 months) during a 4-year follow-up period.[64] Hormonal perturbations during puberty might have contributed to increased insulin resistance and poor glycaemic control.[65] In the SEARCH for Diabetes in Youth Study, researchers reported high BP in 30% and a high LDL-cholesterol in 50% of the non-Hispanic white youths with T2D.[66] In a recent American Diabetes Association position statement, maternal history of diabetes or maternal hyperglycaemia during the child's gestation, family history of T2D, non-Caucasian ethnicity, features of insulin resistance (e.g., polycystic ovary syndrome) and small-for-gestational-age are considered major risk factors for youth-onset diabetes,[67] with the combination of stunted early growth and adolescent obesity being a particularly strong risk factor.[68]

Unlike patients with T1D and adolescent-onset T2D who are often managed in specialist centres by paediatricians, young adults diagnosed with T2D between 18 and 40 years are usually managed in primary care and adult specialist clinics. According to the USA National Health and Nutrition Examination Survey (NHANES), young adults (18–44 years) were less likely to attain a composite $HbA_{1c}$, BP and LDL-cholesterol targets than older adults, and the rates of target attainment had not improved during the 11-year observation period (2005-2008 and 2013-2016).[69] In Asia, despite considerable variations in the attainment of treatment targets across countries, probably reflecting

different quality of the healthcare systems, patients with YOD had consistently worse control of risk factors than their late-onset peers.[52]

Obesity and family history are prominent features in YOD.[70] Despite their non-T1D presentation, patients with YOD often require earlier insulin treatment than those with late-onset disease.[71] In Chinese patients with YOD, 8.1% of patients had glutamic acid decarboxylase antibodies (GADA) suggestive of latent autoimmune diabetes in adults (LADA). While these patients had 60% lower risk of developing CVD, they had greater response to insulin than those without GADA (2.3% versus 0.7% reduction in $HbA_{1c}$), albeit with 60% higher risk of developing severe hypoglycaemia. Compared with patients with classical T1D presentation, patients with YOD and positive for GADA had nearly 3-fold higher risk of ESKD.[72]

The discovery of both common and rare genetic variants including maturity onset diabetes of the young (MODY) due to single gene mutation with high penetrance calls for more precise diagnosis in these young patients. Apart from family screening, identification of these genetic causes have implications for treatment selection with some benefiting from early insulin treatment and others from oral drugs.[73] Adding to this complexity, patients with YOD often have multiple cardiometabolic risk factors, worsened by psychosocial distress[38,74] with poor adherence or frequent clinic defaults.[52,75,76] In a prospective population-based analysis, modelling revealed that by delaying the onset of diabetes or optimising control of all cardiometabolic risk factors, the hospitalisation rates in YOD could be reduced by 30–60%.[40] However, the lack of evidence-based guidelines due to exclusion of these young patients from large randomised clinical trials (RCTs)[77] pose additional challenges in optimising care in these patients. Given their heterogeneous aetiologies, long disease duration and extremely high lifetime risk for life-threatening complications,[59,78] adults with YOD, not dissimilar to T1D, will benefit from inter-disciplinary care in specialist-led diabetes centres for the ascertainment of aetiology (where possible) and intensive risk factor management including lifestyle intervention and psychosocial support, as and when needed.

Indeed, the phenotypic heterogeneity and variable treatment responses are not limited to YOD. In the United Kingdom Prospective Diabetes Study (UKPDS), 12% of adults with T2D had either GADA or islet cell antibodies (ICA) and 4% had both antibodies. These patients with LADA had the most rapid rate of oral medication failure and insulin requirement, especially amongst patients aged less than 45 years.[79] In a multicentre Scandinavian cohort of 8,000 adults with T2D, researchers used GADA, HOMA (Homeostasis model assessment) indices (HOMA %B for beta-cell function and HOMA-IR for insulin resistance, derived from fasting plasma glucose 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 which predict insulin requirement and CKD.[80,81] Using RCT data, other researchers confirmed the prognostic value of these clusters but indicated that the use of specific phenotypes, notably $HbA_{1c}$, age of diagnosis, estimated glomerular filtration rate (eGFR) and BP, outperformed these clusters in predicting treatment responses.[82] Taken together, these findings point to the increasing need to use data more effectively to stratify risk and classify patients in order to personalise care, especially in young patients and those with an atypical presentation.

### *3.3 Abnormal beta-cell biology is a key feature in both T1D and T2D*

Glucose is an important 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 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.[83] While autoimmune destruction of islets is considered the primary event in T1D,[84] abnormal beta-cell biology also plays an important role in T2D. There are considerable inter-individual variations in the weight (0.5–1.2 gram) and number of islets (100,000 to 2.3 million) in humans,[85] with close correlation between BMI and islet mass,[86,87] which are particularly relevant to people living in LMICs such as Africa.

Compared with individuals with normal glucose tolerance, those with impaired glucose tolerance (IGT) had reduced first-phase insulin secretion with compensatory hyperinsulinaemia to correct hyperglycaemia, as well as non-suppression of glucagon during oral glucose ingestion.[88] [89,90] To date, over 400 genomic loci have been discovered in T2D 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 may reflect the overlapping nature of these biological pathways with frequent co-occurrence of obesity, diabetes and other NCDs.[91]

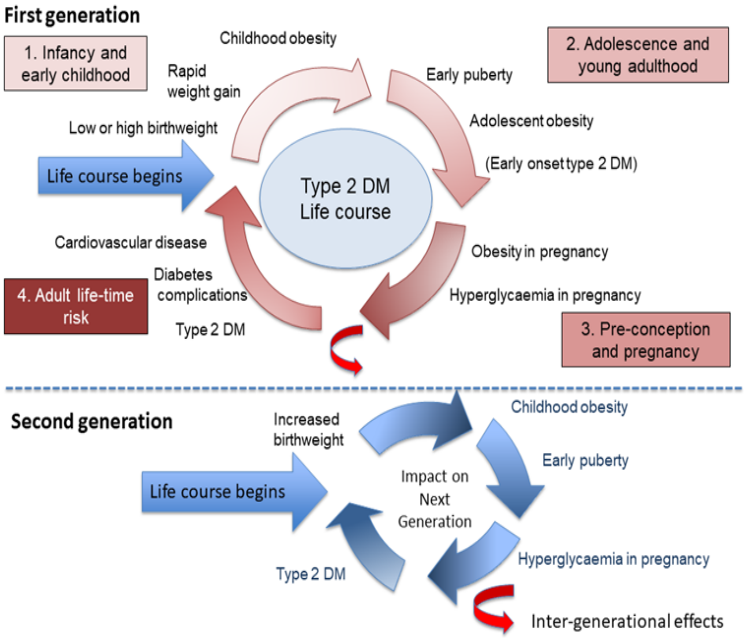
### *3.4 Obesity, maternal hyperglycaemia and perinatal development*

Globally, obesity affected 640 million adults and 110 million children and adolescents in 2014 (10.8% of men, 14.9% of women and 5.0% of children).[92] The prevalence of obesity has doubled in the past three decades, which is mirrored by a similar rising prevalence of diabetes in many parts of the world.[4] Childhood obesity can track into early adulthood and predict ischaemic heart disease in adulthood.[93] The rapid rise in childhood and adolescent obesity may contribute towards the rising trend of YOD and premature NCD, if remedial actions are not taken.[52,94] In a large cohort of Danish men (n=62,565), childhood overweight at 7 year-old was associated with increased risk of diabetes in adulthood only if it continued until puberty or later ages.[95] In the Swedish National Diabetes Register, independent of their countries of origin, those with the earliest onset of diabetes (18–44 years) had a higher BMI, worse cardiometabolic risk factors and a more rapid deterioration in glycaemic control, compared with those with later-onset diabetes.[96]

Epidemiologic evidence for the transmission of diabetes risk to the offspring can be summarised as follows. In the Pima Indian population, risk of developing diabetes was highest in offspring of women with diabetes at conception, followed by offspring of women who developed diabetes after pregnancy, then offspring of non-diabetic women (offspring diabetes prevalence: 45%, 8.6%, 1.4% respectively). Since no increased risk was related to paternal diabetes, these findings highlight the potential contribution of the intra-uterine environment beyond genetic effects.[97]

Data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) follow-up studies showed that offsprings of mothers with untreated gestational diabetes, independent of maternal BMI, had increased risk of obesity and diabetes at age 7[98] as well as increased adiposity at age 10-14.[99] In the SEARCH for Diabetes in Youth Study, participants had a high frequency of parental diabetes and T2D was diagnosed 1.68 years earlier among those exposed to diabetes in utero than among those whose mothers' diabetes was diagnosed later, after adjusting for age of diagnosis of maternal hyperglycaemia, paternal diabetes, sex and race/ethnicity.[99] This is in contrast to paternal diabetes, which was not associated with age of onset of diabetes.[100] In the SEARCH for Diabetes in Youth Study, it was estimated that 47.2% (30.9-63.5) of youth-onset T2D was attributable to maternal diabetes or maternal obesity.[101] Various combinations of high and low birth weight as well as childhood obesity, can result in early age of diagnosis of diabetes. Premature puberty and pregnancy in daughters of mothers with history of gestational diabetes may repeat the same pattern of maternal obesity and hyperglycaemia leading to intergenerational transmission of diabetes (Figure 3).[102]

**Figure 3. Lifecourse development of type 2 diabetes, highlighting the role of different risk factors at different stages of the lifecourse. Adolescent obesity and maternal hyperglycaemia are some of the factors that contribute to risk in the next generation, and perpetuating the rising prevalence of young onset diabetes. There are numerous opportunities for prevention and intervention during the lifecourse. The red curved arrow linking different generations represent a combination of different effects including the effects of maternal hyperglycaemia and obesity (directly via modulating growth as well as through epigenetic mechanisms), altered microbiome, as well as shared genetics and behaviour, environmental exposures (Ma RC and Popkin BM PLoS Med 2017).**




Apart from shared environment, socioeconomic position (SEP) and lifestyles, the unfavourable metabolic milieu starting from pregnancy, along with other external factors, throughout a lifecourse, can affect gene expression (so-called epigenetics) to influence multiple pathways manifested as multiple phenotypes (e.g., obesity, inflammation and beta-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 T2D substantial.[103] Women with maternal obesity and hyperglycaemia are at high risk for developing T2D and CVD. Pregnancy is a great opportunity to influence the future health of mother and child. Integrating maternal and child care including perinatal education and postnatal assessment and advice on individual maternal risks for diabetes can be the first step towards this important goal.[104] Yet, only about 30% of women attend for postnatal glucose testing, which calls for implementation of local strategies to reach most women. User-friendly screening tests such as risk scores, fasting blood glucose and $HbA_{1c}$ can be used to increase the postnatal testing rates in these high-risk women.[105] Taken together, the high prevalence of maternal hyperglycaemia and its potential impacts on future generations, suggest the importance of public health action at early stages of the lifecourse which, by producing results that may go beyond generations, are of far-reaching impact.[106]

## 4 Using 'epidemic' to describe diabetes highlights the importance of environment and behaviour

The word 'epidemic' is often used to describe the global challenge of diabetes. It refers to the phenomenon of 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 (e.g., poor sanitation), an agent (bacteria) and transmission to a susceptible individual (host).[107] Diabetes is a classical example of complex diseases as it has multiple causes, none of which are either necessary or sufficient for disease development.[108] However, the changes in the ecosystem and human behaviour, as prominent features in the current epidemic of diabetes and other NCDs, can be viewed as a complex event due to environment-host interactions, which will require a social-biological strategy.

### *4.1 Ethnicity, socioeconomical development and risk of diabetes and its complications*

Non-Caucasian populations, notably Mexicans, Africans and East Asians, only need a small increase in adiposity to develop diabetes, in part due to insufficient insulin response to compensate insulin resistance associated with weight gain.[89,109] In the USA Multiethnic Cohort, the age-adjusted diabetes prevalence ranged from 6.3% in Caucasians to 10.2% in Japanese, 16.1% in Native Hawaiians, 15.0% in African Americans, and 15.8% in Latinos. After adjustment for other risk factors, the 2-fold higher risk for diabetes amongst non-Caucasians remained in all BMI categories.[110] The marked increase in diabetes prevalence in migrant populations living in modern societies who originated from LMICs, as well as the exponential rise in diabetes prevalence in LMICs with socioeconomic development, highlight the importance of environment-host interactions.[111]

On an individual level, diabetes risk can be further influenced by age, sex, ethnicity, genetics and education level.[3] The impacts of rural-urban migration can be demonstrated in many developing countries. Using India as an example, in a nationally-representative, population-based survey (2012–2014) of 1.3 million adults, the crude prevalence of diabetes and hypertension varied from 3.2% to 19.9% and 18.0% to 41.6%, respectively, with variations by age, state and rural versus urban locations.[112] In another prospective epidemiological survey of 9,848 adults in India, between 2006 and 2016, the most rapid increase in diabetes prevalence occurred in towns (16.4% to 20.3%) and peri-urban villages (9.2% to 13.4%) compared with cities (18.6% to 21.9%), wherein age, family history of diabetes and central obesity were major risk factors.[113]

Given the cross-influence between ecological and biological development, in the early 1990s, anthropologists warned against the potential mismatching between biology and modernisation leading to 'diabetes running wild'.[114] The tendency of non-Caucasians to store fat centrally rather than peripherally contributes to the early development of insulin resistance. Despite their low BMI, this preponderance for visceral fat deposition is often associated with increased lipolysis and inflammatory responses.[115] Many theories have been put forward to explain the global epidemic of diabetes. In the 'capacity-load model', imbalance between 'metabolic load' (e.g., 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 inability to maintain metabolic homeostasis 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 may be particularly relevant to LMICs.[116]

Other researchers have hypothesised that genetic traits and/or phenotypes that promote efficient energy storage and/or activation of the stress and inflammatory responses might confer survival advantages in a food-deprived, physically strenuous and pathogen-rich environment.[117] Thus, people with ancestors who led a subsistent lifestyle may have a phenotype of low BMI closely correlated with beta-cell mass[87] while strenuous physical activity and external stressors such as infections may encourage storage of visceral fat for efficient release of free fatty acids and cytokines. These combined traits of insulin resistance and relative insulin insufficiency may be particularly relevant to populations that undergo rapid nutritional and lifestyle transitions.[62,118,119] To this end, increased activity of the sympathetic nervous system, hypothalamus-pituitary-adrenal axis, renin-angiotensin system (RAS) and innate immunological responses have been reported in T2D. Together with ageing characterised by reduced secretion of growth hormone, insulin-like growth factor 1 and sex steroids which can lead to reduced lean body mass and increased adiposity, multiple subphenotypes including obesity, metabolic syndrome, cardiovascular–renal dysfunction and possibly cancer, all of which share common biological pathways, may emerge.[62,120,121]

### *4.2 Changing demographics, environment and ecosystem*

The demographic ageing transition,[4] along with increasing obesity[92] and physical inactivity,[122] are driving the global epidemic of diabetes. 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 amongst 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 the diet favouring more sugar-sweetened beverages and sodium but with fewer grains, fruits and vegetables, increasing portion sizes and changing work schedules, which in turn alter dietary patterns and sleep schedules. In LMICs, food insecurity, poor affordability for healthy foods (e.g., fresh fruits, vegetables, whole grains) with undernutrition and high consumption of low-quality calories are not uncommon, often made worse by poverty.[111,123] Similarly, in HICs, underserved communities often have limited choices of leisure activities and tend to consume more energy-dense food and often cannot afford healthy foods which tend to be expensive.[124,125] In the latest GBD 2017 analysis, dietary factors explained as much as 20% of the attributable risk of NCD.[126]

Environmental pollutants, many of which are endocrine disruptors, such as bisphenol A, have also been implicated in causing diabetes, obesity and cardiovascular-renal diseases.[127,128] These environmental factors may be particularly relevant in LMICs where the prevalence of obesity is lower than that in Western countries.[129] Other reports have highlighted the impacts of extreme temperature in increasing the risk of CVD events in people with diabetes.[130] Social problems arising from rapid rural-urban migration such as overcrowding, social isolation/disparity and psychosocial stress may 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. While these factors may theoretically contribute to the development of diabetes, more research is needed to quantify the impacts of these societal changes on health and diseases, including but not limited to, diabetes and other NCDs in different populations living in different environments.[13]

### *4.3 Multimorbidity of diabetes including acute and chronic infections in LMICs and underserved communities*

The interactions between chronic infections, notably tuberculosis, and NCDs such as diabetes, are particularly relevant to LMICs such as India, Africa, Mexico, which are hit by these double burdens.[131] Together with the emerging evidence regarding the damaging effects of coronavirus on beta-cells, there is a possibility of worsening of the diabetes pandemic against the backdrop of the COVID-19 pandemic.[132] These two pandemics are likely to hit the LMICs and underserved communities in HICs the hardest. The multimorbidity of diabetes in subpopulations and communities within a socioeconomic and cultural context highlight the considerable heterogeneity of disease predisposition, clinical patterns as well as social and medical needs, which will require a multidimensional strategy.[114]

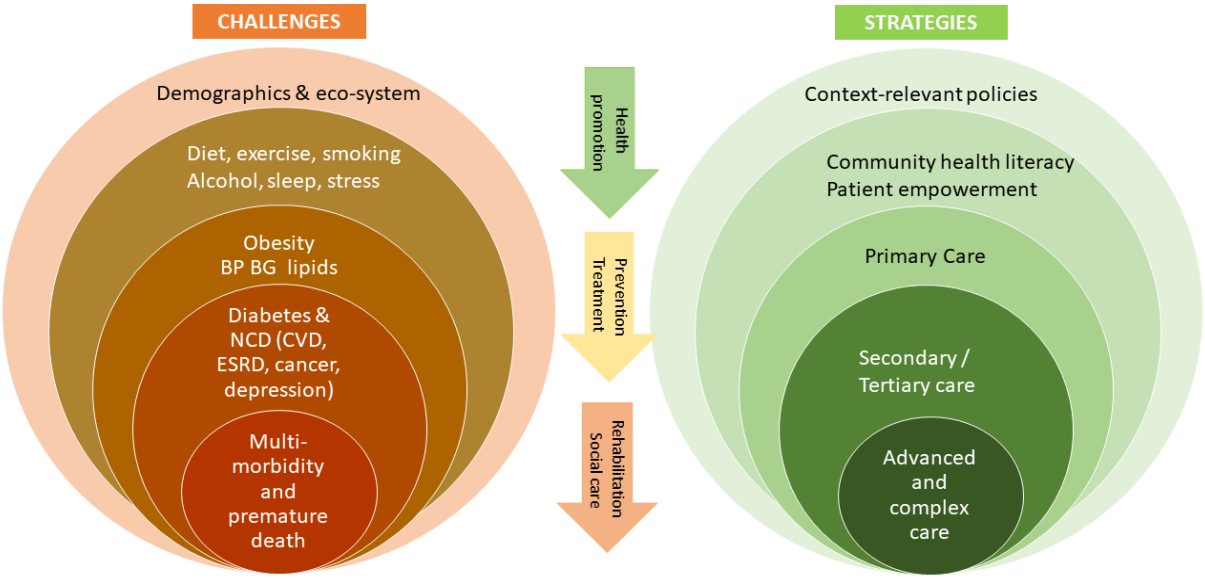
Infections aside, researchers have reported independent associations of obesity, diabetes and CVD with low educational levels and SEP, which contribute towards unhealthy lifestyles.[133,134] In Scotland, in a population-based cohort, life expectancy in people with T2D was reduced at all ages and levels of SEP with loss of 5.5 years in women aged 40-44 in the second most deprived quintile of SEP.[135] In the USA, diabetes-related mortality are closely associated with low-income status, low educational level and non-Europid ethnicity.[136] Within the workforce, long working hours, poor sleep hygiene and shiftwork were associated with increased risk of obesity and diabetes.[137,138] Low education might interact with high personal income to increase the risk of diabetes in population whose affluence has changed recently.[139] In LMICs, the rural-urban migration and social mobilisation especially amongst the young, may be accompanied by other stressors which can lead to risk-conferring behaviours such as the use of tobacco and binge drinking. In China, while high income and high education level were associated with increased risk of diabetes in men, high education level was associated with reduced risk of diabetes with income having little or no effect size in women.[140]

The clustering of these risk factors are further modified by socio-anthropological factors such as geo-physical environment, family SEP, age of migration, levels of acculturation and adaptation to new cultures. Indeed, the social gradient of diabetes in LMICs can be complex. It depends on the specific measure of SEP, as well as the level, speed and pattern of economic development. The gradient may be positive in some countries and for some measures of SEP, can be negative in others,[141-143] where lower SEP may be associated with a more physically-active lifestyle and less access to excess dietary calories. The frequent clustering of diabetes, depression and poverty in LMICs as well as 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 as 'syndemic'.[144,145] The impact of COVID-19 with high rates of death, amongst not just those with diabetes but also certain communities such as African Americans and minor ethnicities, where inequalities, poor access to care, comorbidities often prevail, is a wakeup call regarding the need to protect the vulnerable for common good.[146]

To this end, the recent Lancet Commission Reports on the close links between climate change, food systems and global epidemic of obesity and NCD[147,148] remind us once again of the fragility of human health in a rapidly changing ecosystem,[149] which calls for an integrated socio-biomedical approach to protect health and prevent disease (Figure 4). In recognition of these societal determinants of NCD, in the recent United Nations Health Summit, environmental protection and mental illness have been included as top agenda items in the fight against NCD.[150-152]

**Figure 4: The environment-lifestyle-host interactions underlie the complex nature of diabetes and NCD which requires a combination of personal and societal strategies by using context-relevant policies and system change in order to cover the full spectrum of health promotion, prevention, treatment, rehabilitation, and social care (refer to Table 1 and section 7.1).**




## 5 The healthcare and societal costs of diabetes

The disproportionately higher rate of increase in healthcare expenditure compared with that in Gross Domestic Product (GDP) are in part due to ageing, rising costs of technology and increasing expectation from patients and public. This discrepancy between earning and spending calls for better healthcare planning and more cost-effective use of finite resources.[153] In 2016, global spending on healthcare was USD 10.3 trillion (purchasing power-adjusted) in total or USD 1,400 per capita.[154] The respective per capita healthcare spending has increased at an annual rate of 4.0% from 1995 to 2016. This spending is expected to continue to increase to USD 2,373 per capita by year 2040, at a rate which exceeds the growth of national income.[155]

Around one-tenth of global healthcare expenditure was devoted to the treatment of diabetes, mainly for treatment of its complications and comorbidities. In 2017, the cost of care for people with diabetes accounts for 1 in 4 healthcare dollars in the USA, an average of USD 16,750 which is 2.3-fold higher than for an individual without diabetes.[156] In the USA with predominantly private healthcare, individuals with diabetes and ischaemic heart disease, congestive heart failure, hemiplegia and amputation had 50–70% higher costs, and those with ESKD with renal transplant had 500% higher cost than those without complications.[157] In a recent report from Italy where healthcare is largely publicly-funded, researchers used a simulation model and estimated the average yearly costs per patient with diabetes could rise from USD 382 in those without morbidity to USD 7,937 in patients with coronary,

cerebrovascular, renal and retinal complications.[158] Irrespective of the number of comorbidities, over 70% of the costs were due to hospitalisation. Two-thirds of direct healthcare expenditure was due to treatment of complications, with outpatient care and medications accounting for a smaller proportion of the total costs.

Apart from direct medical costs which include outpatient and inpatient services, emergency care, medications, laboratory tests, medical equipment and supplies as well as long-term care, people with diabetes may have reduced work performance. They may also miss more workdays due to health condition, and their working lives may be cut short by permanent disability and premature death.[159] The productivity loss due to the shorter working lives, sick leave (absenteeism) and reduced work performance (presenteeism) are indirect costs of diabetes. If a large population of young individuals are affected by diabetes which increases the risk of premature death and morbidity, their productive potential will be reduced, resulting in reduced growth of national economies. The loss of earning can lead to a vicious cycle where diabetes aggravates poverty which can worsen access to care, poor outcomes and low productivity.

Individuals in LMICs and to some extent, underserved individuals and their families in HICs, often have low levels of awareness and face greater 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, while some 70% of individuals with diabetes lived in LMICs, more than 90% of the global expenditure was in HICs. There are also enormous variations in healthcare expenditure on diabetes ranging from 2% in Rwanda to 41% in Nauru of a country's total healthcare expenditure.[160] To this end, the 2–3 fold higher and rising incidence of CVD and death rates in LMICs (e.g., India) as compared with the declining rates of CVD in North America and Europe suggested the need to invest more in preventive care in LMICs, which have the least affordability to pay for expensive treatment for late complications.[40]

In 2015, the estimated global indirect cost of diabetes was USD 294 billion or 35% of the total economic burden of diabetes. Of the total indirect cost, 94% was due to either premature death or dropout from employment due to disability. In LMICs, over 64% of indirect cost was from premature death and 60% in HICs. Individuals with diabetes in LMICs tend to die at a younger and productive age than their counterparts in HICs.[161] The global economic burden of diabetes is expected to increase due to the growing population of diabetes and the increase in per capita medical expenditure for diabetes. The projected total global economic cost due to diabetes was predicted to increase from USD 1.3 trillion (1.8% of global GDP) in 2015 to USD 2.2 trillion (2.2% of global GDP) in 2030. The direct medical cost would increase from USD 0.86 trillion to USD 1.70 trillion, while the indirect cost would increase from USD 0.46 trillion to USD 0.78 trillion.[162]

From a value perspective, the substantial amount of resources used to treat diabetes and its complications could be used for other productive activities including diabetes prevention measures.[163] Some studies have simulated the impact of diabetes on GDP at the country level or globally. Predictions have shown that global GDP might have been USD 1.7 trillion higher from 2011 through 2030 if diabetes had been eliminated in 2010. While such losses would be borne largely by HICs (53% of total), the predicted GDP loss for China was USD 49 billion and for India was USD 15 billion.[161] Another study estimated that Finland's GDP would be 1.1% higher if diabetes were eliminated.[164]

## 6 Access to care, education and medications in T1D

In HICs, the major current focus in T1D is on reducing the treatment gaps in the prevention of micro/macrovascular complications as the leading cause of death.[165] The situation is far worse in LMICs where poverty and lack of infrastructure and professional knowledge often lead to limited insulin availability with poor access to diabetes education. As a result, children with T1D often have an extremely poor outlook, they are frequently misdiagnosed, develop acute and chronic complications, and die prematurely.[166-168] Competition between manufacturers has led to the availability of relatively

inexpensive insulin products, which should be part of the essential medicines list in all LMICs as recommended by the WHO and made affordable and available with appropriate use.[166,167,169,170]

### *6.1 Ensuring access to insulin and patient education to improve self-management*

A particular concern for those with T1D is the high level of training needed for HCPs, not just physicians but also nurse educators, dietitians and social workers. In turn, tailored diabetes education of patients and relevant family members is important, covering not just insulin and self-monitoring of blood glucose (SMBG), but also diet (preferably with carbohydrate counting), exercise and other factors.[171] Attention needs to be given to the time at school for children, addressing stigma, managing 'sick days', as well as dealing with issues of adolescence including contraception and pregnancy planning. Education materials should be culturally sensitive and written accessibly. The period of transition of a young individual to adulthood with utilisation of adult healthcare services is a pivotal time that needs locally-adapted and effective programmes.[172] Monitoring and benchmarking efforts are key to achieving improved care, and international benchmarking efforts are available. By highlighting different outcomes between clinics in similar situations, this can provide the impetus for improving the organisation and quality of care.[173,174]

Insulin analogues are now widely used in many countries. Basal insulin analogues are better than human or animal (bovine and porcine sources) insulins for minimising the risk of nocturnal hypoglycaemia and are particularly useful for basal-bolus regimens (multiple daily injection therapy involving a long-/intermediate-acting insulin and short-/rapid-acting insulin at each meal).[175,176] That said, human and biosimilar insulins are more affordable insulins in low-income areas.[177,178] In T1D, basal-bolus insulin regimens offer better glycaemic control than twice-daily regimens, if accompanied by appropriate education of individuals with diabetes, family and care providers with access to adequate supplies of needles, lancets and testing strips for performing SMBG. However, the cost of SMBG is often higher than that of insulin.[179] In some LMICs, the tariffs on insulin and SMBG supplies often reduced the affordability of these treatments.

Many clinics are still using twice-daily insulin regimens, often with premixed insulin.[166] These regimens are usually associated with higher $HbA_{1c}$ and more frequent hypoglycaemia, especially when used with little or no SMBG and diabetes education, although other non-insulin determinants of quality of glycaemic control are also important.[180] In these settings, we have observed that due to limited insulin, food insecurity, unavailability of SMBG and glucagon (to reverse hypoglycaemia) and lack of transport and emergency services, there is a tendency to reduce the dosages of premixed insulins. All these factors can increase the risk of poor glycaemic control and complications which can adversely affect growth and quality of life.[172] Even in HICs, poverty, varying healthcare financing or insurance policies, lack of price transparency, complexity in supply chains and insufficient competition amongst a few manufacturers have made insulin and SMBG supplies difficult to afford.[181,182]

### *6.2 Use Diabetes Centres to build capacity and improve care standard in T1D*

The global impact of T1D can be diminished through more 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, healthcare providers must be taught how and when to measure blood glucose in sick children (to prevent death from misdiagnosis) and habituated to doing so as a matter of routine.[168,172,180,183] The establishment of Specialised Diabetes Centres or regional T1D Centres in LMICs provide a focal point for building capacity to improve management of acute emergencies and complex problems (see also Section 9.7). Extra support may 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-hour emergency advice. Peer support also offers potentially profound advantages. While models of care should be adapted to each country's available resources and healthcare system, they should aim to provide at least 'Intermediate Care' as per the 'Levels of Care' (Panel 1), either at no cost to patients, or at a cost affordable to all.[180]

In some countries, programmes such as the Life for a Child,[184] Changing Diabetes in Children[185] and Insulin for Life[186] with in-kind support from pharmaceutical industries and expert volunteers, have

significantly improved care and outcomes.[167] Patient and family education resources such as videos, graphic novels and Conversation Maps (an innovative facilitator-guided group education tool which uses maps to help patients come to terms with living with diabetes) simplified treatment guidelines, while two African training colleges for paediatric endocrinologists are now available. However, many of these programmes are supported by one-off philanthropic donations. Improvement of health systems within countries could provide a more sustainable support system that could have long-term benefits on the health outcomes of children with T1D.

### *6.3 T1D Registers reveal a secular improvement, but with major care gaps*

Although many registers of childhood-onset T1D exist, documentation of the overall burden arising from T1D remains incomplete. There are two main deficiencies. Firstly, incidence and prevalence data from many parts of the world, notably Sub-Saharan Africa, are very limited. Secondly, few studies have focused on adult-onset T1D. The incidence of childhood-onset (<15 years of age) T1D was extensively reported in the landmark DIAMOND study, initiated by the WHO in 1990. The report included data from 112 registers in 57 countries and suggested a 400-fold variation in annual incidence, ranging from 0.1 per 100,000 (China and Venezuela) to 40.9 per 100,000 (Finland).[187] Some of this difference may be due to lack of recognition of cases in less-resourced countries, but up to 30-fold differences in incidence have also been observed amongst HICs, e.g., between Finland and Japan.[3]

However, 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 those aged 10–14 years. There was a male preponderance in high-risk countries and a female excess in low-risk countries. In European countries, incidence had risen by about 3% per year from 1989 to 2003,[188] although this rise appears to be slowing in high-risk countries like Finland,[189] Norway[190] and amongst non-Hispanic whites in the USA.[191] These trends are in contrast to low-risk countries and populations like China,[192] Korea[193] and amongst Hispanics in the USA,[191] where higher rates of increase were seen. Striking increases in apparent incidence may also occur in lower-income countries in part due to increased ascertainment as care improves.[168] In 2017, the International Diabetes Federation (IDF) estimated there were 1.1 million children and adolescents aged less than 20 years with T1D.[3] In adults, the few studies available suggest that, although the incidence of T1D was somewhat lower than that seen in adolescents, it continued to occur throughout adulthood. In Sweden, the incidence of T1D fell from 37 per 100,000 before age 20 years to 27 per 100,000 thereafter, and the rates for those aged 70–79 were higher than for those aged less than 9 years.[194] These findings underscore the importance of more extensive data and studies of T1D in adults despite the difficulties in typology (classification), which is a significant barrier without extensive laboratory testing.

The burden of T1D reflects not just its prevalence and management requirements but also the consequences of the long-term risk of major complications (visual loss, foot ulcers, CVD, lower extremity amputation, diabetes-related death) (Figure 5A). These data are from the Pittsburgh, Pennsylvania (USA)-based Epidemiology of Diabetes Complications (EDC) study. After 30 years of exposure to hyperglycaemia, nearly 80% of patients with T1D suffered one or more of the above complications. Although visually, the bar charts suggest declining incidence of complications across the different cohorts, none of these trends were significant indicating no improvement in these complications rates overtime. These data highlight the urgent need to further improve clinical management, particularly for hypertension, as reported in another EDC subanalysis.[195]

In HICs such as Australia, the death rate in patients with T1D is less than 2 per 1000-person-years. By contrast, recent reports from Africa and Central Europe indicate that rates are 9 or more fold higher (Figure 5B). In the USA and Europe, and in places like Taiwan which generate high-quality national data, life expectancy of patients with T1D has improved over time, although an individual with T1D may still lose up to 17 years of life compared with the general population.[196] To put this figure into perspective, patients diagnosed 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 these HICs, such improvements have not been seen in LMICs. A loss of 28 years of life was estimated in Mali in the early 1990s.

On the other hand, social disparity remains a major barrier to care in HICs. Between 1979 and 1984, among African Americans in the USA, T1D was associated with 30 years loss of life expectancy as compared with 20 years loss in the general population.[197] Although the survival rates have improved in recent years, the gap between African Americans and the general population persisted.[165] In Scotland, from 2006-2010 to 2011-2015, the age-standardised mortality rate per 1,000 person-years in people with T1D had declined from 24.8 to 20.4 in men and from 22.5 to 17.6 in women. However, during the same period, the rate ratios for the most versus least deprived groups had increased from 2.49 to 2.81 in men and from 1.92 to 2.86 in women.[198] These marked variations in T1D survival over time between countries and within countries highlight the impact of national socioeconomic development and social/care disparity on clinical outcomes, even in HICs.[199-201]

**Figure 5A. Cumulative incidence of diabetes-related complications and related death within the examined Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort of childhood-onset type 1 diabetes, according to calendar year of diagnosis. The p values highlight the lack of improvement of these trends within each age group diagnosed during different time periods.**

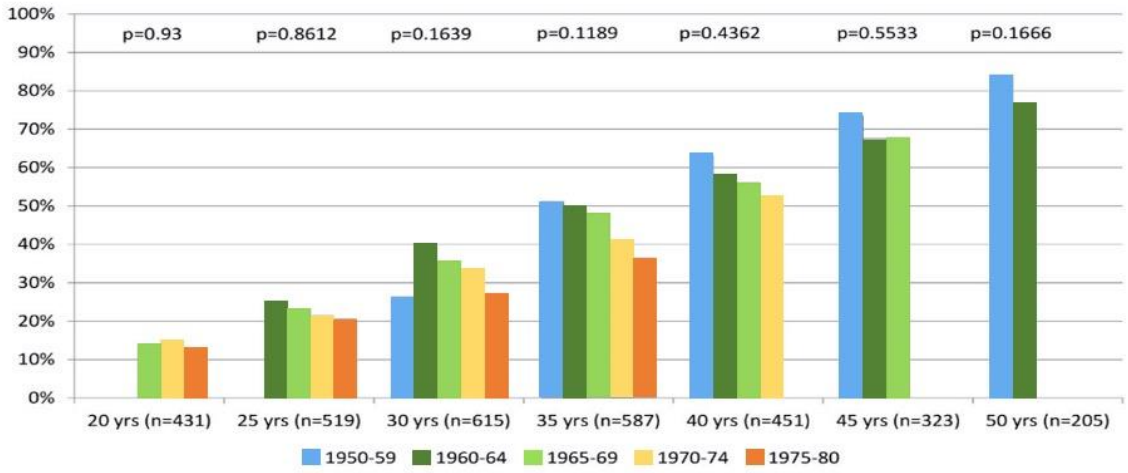
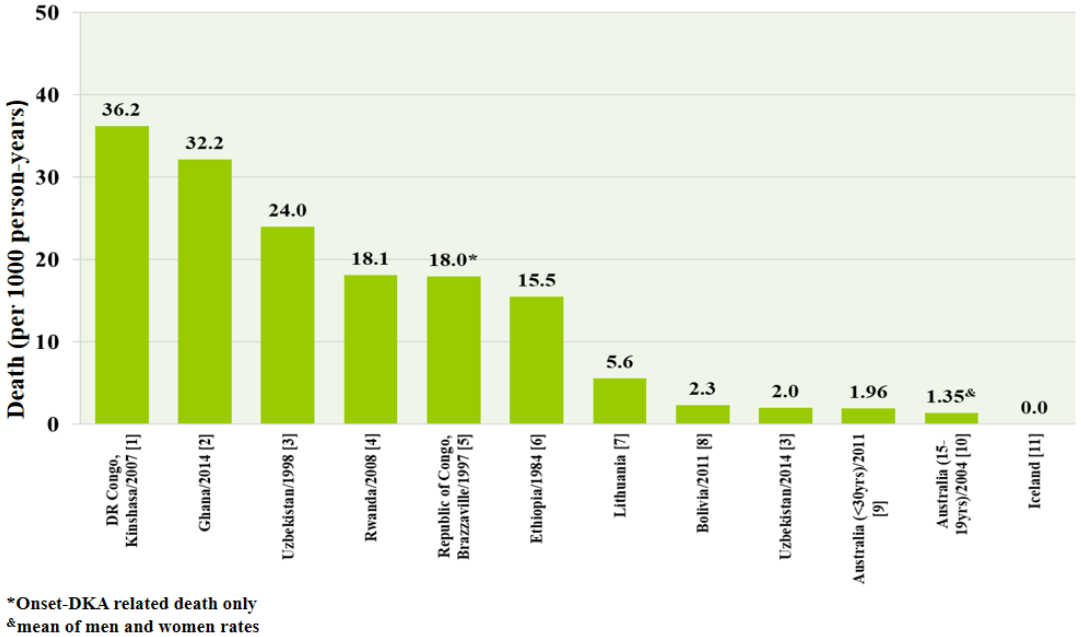



**Figure 5B. Premature death in patients with type 1 diabetes diagnosed before the age of 40 years in different countries (refer to supplemental text for details of references).**




*Onset-DKA related death only
&mean of men and women rates

### *6.4 Standardised mortality ratio and excess deaths in young individuals with T1D due to care gaps*

In HICs, quality care (defined as 'guideline-based comprehensive' care) is generally provided to young individuals with T1D. In contrast, most young individuals in low-income, low-to-middle-income and many young individuals in upper-middle-income countries receive 'minimal' or 'intermediate' care (Panel 1).[180] We estimated the excess mortality due to this care gap in individuals aged less than 25 years and diagnosed with T1D before the age of 20. This was done by searching the literature for mortality data in young individuals with T1D diagnosed during childhood or youth, wherein the SMR was stated or could be calculated by comparing the stated mortality rate to background mortality using the WHO lifetables data. Eighteen studies were identified on comprehensive care from HICs, three on intermediate care from upper-middle-income countries, seven on intermediate care from lower-middle and low-income countries (pooled), and one each on minimal care from lower-middle and 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, estimated SMR 13.6) and low-income countries (50% minimal and 50% intermediate, estimated SMR 33.9).

Using incidence data of T1D from the IDF, population data and background mortality rate from the United Nations,[202,203] as well as age of diagnosis reported in different studies, we developed a discrete time Markov illness-death model[204] with age-dependent transition probabilities for all 220 countries listed in the IDF Atlas. We estimated that globally 14,466 young individuals with T1D died in 2017, from a total prevalence of 1.61 million. If all patients in LMICs received an intermediate level of care with reduced SMR, 8,369 deaths could have been averted (58% of all deaths). This number increased to 12,092 if all nations were to implement guideline-based comprehensive care resulting in a further reduced SMR (84% of all deaths averted) (refer to Supplemental Material).

## 7 Reduce diabetes-related complications by reducing multiple risk factors

In the last three decades, prospective cohort analyses have reported the risk associations of BP, blood glucose, LDL-cholesterol with CVD and death in T2D.[205-207] This was followed by large-scale RCTs which demonstrated that sustained reduction of these risk factors for 2–5 years could substantially improve clinical outcomes in T2D. Subsequent meta-analysis of these RCTs results confirmed that reduction of $HbA_{1c}$ by 0.9% (10 mmol/mol),[208,209] systolic BP by 10 mmHg[210] and LDL-cholesterol by 1 mmol/L (39 mg/dL)[211] individually reduced the risk of CVD and/or all-cause death by 10–20%, independent of other risk factors. In a meta-analysis, it was estimated that for every 200 patients with T2D treated for 5 years, 14 events of myocardial infarction can be prevented with reduction of 4 mmHg in systolic BP, 8 events with 1 mmol/L (39 mg/dL) reduction in LDL-cholesterol and 3 events with 0.9% (10 mmol/mol) reduction in $HbA_{1c}$.[208] Given the important role of activation of RAS[212] in causing cardiovascular-renal diseases, landmark studies have also confirmed the protective effects of RAS inhibitors (RASi) in both T1D[213] and T2D,[214-216] especially in the presence of increased albuminuria.

### *7.1 Use multifactorial management to achieve multiple treatment targets*

Several RCTs have examined the control of multiple risk factors on cardiovascular-renal events and all-cause death, such as the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care), Steno-2, J-DOIT3 (Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases) and SURE (Structured Versus Usual Care on Renal Endpoint in Type 2 Diabetes) trials. In the ADDITION trial, individuals were actively screened for T2D 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.[217] In the Steno-2 Study, multifactorial management including lifestyle intervention; control of blood glucose, BP and LDL-cholesterol; as well as use of RASi and aspirin (as appropriate) in patients with T2D and microalbuminuria without a history of cardiovascular-renal diseases, reduced micro/macrovascular complications after 7.8 years. This translated into a long-term reduction in ESKD and all-cause death,

10–20 years after completion of the trial.[218,219] The number needed to treat (NNT) was 5-8 for death from any cause, death from cardiovascular causes, myocardial infarction and stroke over 13 years. The NNT for amputation was 10.[218] Subsequent economic analysis confirmed the cost-effectiveness of this multifactorial intervention when implemented in a primary care setting.[220]

In the SURE study involving patients with T2D and CKD, after receiving 2 years of team-based care with predefined processes aimed at controlling multiple risk factors, the structured care group were 3-fold more likely to achieve multiple treatment targets with persistent use of RASi than the usual care group. After just 2 years, patients who attained 3 or more treatment targets had 50% reduction in ESKD and all-cause death compared with usual care.[221] Similarly, analysis of real-world databases has indicated the proportional and additive benefits of controlling $HbA_{1c}$, BP and LDL-cholesterol on reducing cardiovascular-renal diseases in T2D, with LDL-cholesterol lowering by statins having the greatest effect size.[222-224] In the latest analysis of the Swedish National Diabetes Register involving over 200,000 patients with T2D, there were linear relationships between the number of cardiometabolic-renal-behavioural risk factors attained (defined as $HbA_{1c}$<7.0% [53 mmol/mol], BP<130/80 mmHg, LDL-cholesterol<1.8 mmol/L (70 mg/dL), lack of smoking and microalbuminuria) and cardiovascular events and related death.[225,226]

### *7.2 Stratify risk to maximise benefits and minimise harm of blood glucose lowering*

In the UKPDS started in 1977,[227] achieving an $HbA_{1c}$ difference of 7.9% versus 7.0% (63 versus 53 mmol/mol) in T2D with conventional and intensive glycaemic control strategies respectively and similarly, that of 9.0% versus 7.0% (75 versus 53 mmol/mol) in T1D in the Diabetes Control and Complication Trial (DCCT) started in 1983,[228] reduced the risk of microvascular complications in the short-term and cardiovascular complications in the long-term. Post-hoc analysis identified the close relationship between $HbA_{1c}$ and diabetes-related complications which provided the premise for the conduct of three landmark studies in 2000, which aimed to achieve lower $HbA_{1c}$ values than seen in the UKPDS and DCCT studies.

In all three trials, namely ACCORD (Action to Control Cardiovascular Risk in Diabetes),[229] VADT (Veterans Affairs Diabetes Trial)[230] and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trials,[231] the majority of participants were over the age of 60, had over 10 years of diabetes with multiple risk factors and complications. All three trials had similar design and outcome measures and an achieved mean $HbA_{1c}$ of 6.4%-6.9% (46-52 mmol/mol) during the trial period. Although all three trials confirmed reduced risk of microvascular complications in the intensively-treated group, the results for cardiovascular death were controversial with premature discontinuation in the ACCORD study due to unexpected increased risk of death in the intensively-treated group. This has triggered intensive research which highlighted the high risk of hypoglycaemia in patients with multiple morbidities especially CKD after long disease duration. The silent deterioration of renal function coincides with progressive atherosclerosis in patients with long disease duration. The frequent coexistence of CVD and CKD put these patients, who often receive complex therapies, at high risk of hypoglycaemia which may precipitate CVD or identify patients with a 'frail' phenotype.[232-234] These observations have led to the changes in practice guidelines calling for regular assessment of risk factors and complications for individualisation of treatment targets and strategies in blood glucose lowering, taking into consideration the demographic, biomedical, cognitive, psychosocial and behavioural profiles of patients in order to maximise benefits and minimise harm.[235-237]

### *7.3 Use blood glucose lowering drugs effectively - old versus new drugs*

Together with insulin first discovered in 1922, metformin and sulfonylurea (SU) discovered in the mid-1950s, have been the standard blood glucose lowering drugs which are effective, albeit not without side effects. On average, except for insulin which can lower blood glucose considerably, most of these medications reduce $HbA_{1c}$ by 0.5 to 1% (5.5-11 mmol/mol) although there are considerable inter-individual variations for a single drug, depending on other factors pertinent to hosts and settings.[238] Patients with high $HbA_{1c}$ often have the greatest response, in part, by ameliorating the effects of glucotoxicity on beta-cell function. However, these patients also have the most residual glycaemic burden requiring additional interventions.[239] Using data from long- and short-term trials, researchers

have reported strong correlations between cumulative glycaemic exposure and clinical outcomes, as well as between differential glycaemic exposure and cardiovascular risk reduction. Thus, if blood glucose lowering could be initiated early and sustained with low risk of hypoglycaemia, long-term benefits should ensue even with traditional drugs such as metformin and SU,[240] as indeed reported by the UKPDS.[227]

Insulin and SU have potent blood glucose lowering effects but can cause significant hypoglycaemia which may lead to hospitalisations,[233,241,242] morbidity and premature death, especially in patients with frailty and multiple morbidities.[243] This has led to the emphasis of periodic assessments and education to deliver patient-centred, individualised care, taking into consideration the risk of hypoglycaemia, comorbidities, obesity and economics. During the last three decades, the pharmaceutical industry has invested heavily to develop new medications to lower blood glucose 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.[244] Suffice to say, this diversity reflects the complex regulation of glucose homeostasis involving multiple pathways which have led to the development of a large number of blood glucose lowering drugs with different extra-glycaemic effects.

Amongst different classes of drugs, the cardiovascular-renal protective effects of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP1-RA), independent of blood glucose lowering, have now been confirmed, giving us additional armamentarium in managing these high-risk patients.[245] However, the high price of these new medications have limited their affordability in low-resource settings. Meanwhile, the efficacy, safety and low cost of metformin as well as the cardiovascular safety of SU when compared with dipeptidyl peptidase-4 inhibitors (DPP4i),[246] have reassured the community regarding the clinical value of metformin and SU that are widely used in LMICs.[247] As new medications such as SGLT2i, DPP4i and GLP1-RA become more affordable, the landscape of use of blood glucose lowering drugs may change, considering their organ protective effects, glycaemic durability and long-term cost-effectiveness.[248] In this light, young patients who face decades of hyperglycaemia with high risk of developing complications during their mid-age[53] warrants special consideration. In these young patients, delaying the onset of diabetes and intensifying glycaemic control using drugs with low risk of hypoglycaemia and weight gain may benefit most from these new medications, although evidence from RCTs is needed to inform treatment guidelines.[77]

### *7.4 Diagnose and treat early to induce diabetes remission and improve glycaemic durability for better outcomes*

Reduced early phase insulin secretion and non-suppression of glucagon[88] followed by progressive decline in beta-cell function[249] is a hallmark in IGT and T2D. In the UKPDS, age of diagnosis, obesity (general and central), baseline plasma glucose and triglyceride were predictors of progressive beta-cell failure and treatment escalation.[250] In a proof-of-concept study, researchers have reported sustained recovery of insulin secretion at 2 years after 2 weeks of intensified insulin treatment in T2D.[251] In the Diabetes Remission Clinical Trial (DiRECT), a primary-care led weight management programme involving patients with T2D with less than 6 years of disease and a BMI of 27-40 kg/m$^2$ (mean BMI 35.1 kg/m$^2$), 149 were randomised to receive intervention with severe and structured dietary restriction and 149, usual care. At year 1, 46% in the intervention group had diabetes remission (defined as $HbA_{1c}$<6.5% [48 mmol/mol] without medications) and 24% had at least 15 kg of weight loss. Amongst patients with weight loss of 15 kg or more, 85% had diabetes remission. At 2 year, 17 (11%) in the intervention group and three (2%) in the control group had weight loss of at least 15 kg, whilst 53 (36%) in the intervention group and five (3%) in the control group had diabetes remission. In a post-hoc analysis of the whole study population, of those participants who maintained at least 10 kg weight loss (45 of 272 with data), 29 (64%) achieved remission; 36 (24%) of 149 participants in the intervention group maintained at least 10 kg weight loss.[252] Using arginine stimulation test, patients who had diabetes remission exhibited similar peak and first insulin response compared with individuals with normal glucose tolerance, suggesting restoration of beta-cell function after significant weight reduction.[253] Despite these encouraging results, the sustainability and long-term impact of intensive weight loss interventions on remission needs continued study.

Although many patients with diabetes have obesity, some are non-obese[254] in whom early amelioration of glucotoxicity may improve glycaemic durability. In the VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) Study, researchers compared the strategy of early intensive treatment using combination therapy of metformin plus DPP4i versus metformin monotherapy in newly-diagnosed patients with T2D in reducing the likelihood of primary and secondary treatment failure. In this 5-year study involving 2,001 patients with T2D who had a disease duration of 3 months and a mean $HbA_{1c}$ of 6.7% (50 mmol/mol) and mean BMI of 31 kg/m$^2$, combination therapy reduced the risk of poor glycaemic control ($HbA_{1c}$>7% [53 mmol/mol] on 2 occasions 3 months apart) by 49% compared with monotherapy. The time to poor glycaemic control was 36 months in the monotherapy group compared with 61 months in the combination group. With early intensified treatment, these patients were 27% less likely to require insulin therapy compared with the monotherapy group who subsequently also received DPP4i.[255]

The glycaemic legacy effect of early intervention in newly-diagnosed patients in UKPDS[227] and individuals with IGT in a diabetes prevention programme[256] has led to long-term reduction of cardiovascular-renal events and all-cause death. Together with the results from DiRECT and VERIFY studies, the use of a system-wide strategy to diagnose and treat patients with T2D early and intensively may induce remission or maintain glycaemic durability with long-term benefits in addition to the use of other medications for organ protection.

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

In addition to smoking, BP, LDL-cholesterol, $HbA_{1c}$ and body weight are amongst the most modifiable risk factors in diabetes. However, the latter two require considerable behavioural changes and self-management. The results of the DiRECT study led by primary care physicians indicated that significant weight reduction with discontinuation of multiple medications is possible,[257] if patients are given adequate support and supervision. While these results are extremely encouraging, many patients with T2D have long disease duration or poor beta-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 aetiologies of T1D and T2D, once 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 depending on disease stage and treatment.[258] Without proper professional training and structured patient education and support, patients and HCPs alike, will find it difficult to explain these blood glucose fluctuations and take corrective actions. Patient dissatisfaction and distress can lead to frustration and burn out for HCPs resulting in poor patient-provider relationships, which in turn may worsen treatment adherence and quality of care.[35,39,259] Training of HCPs in psychological health and behavioural science will help them design, implement and evaluate patient empowerment programmes needed to promote self-management.[260]

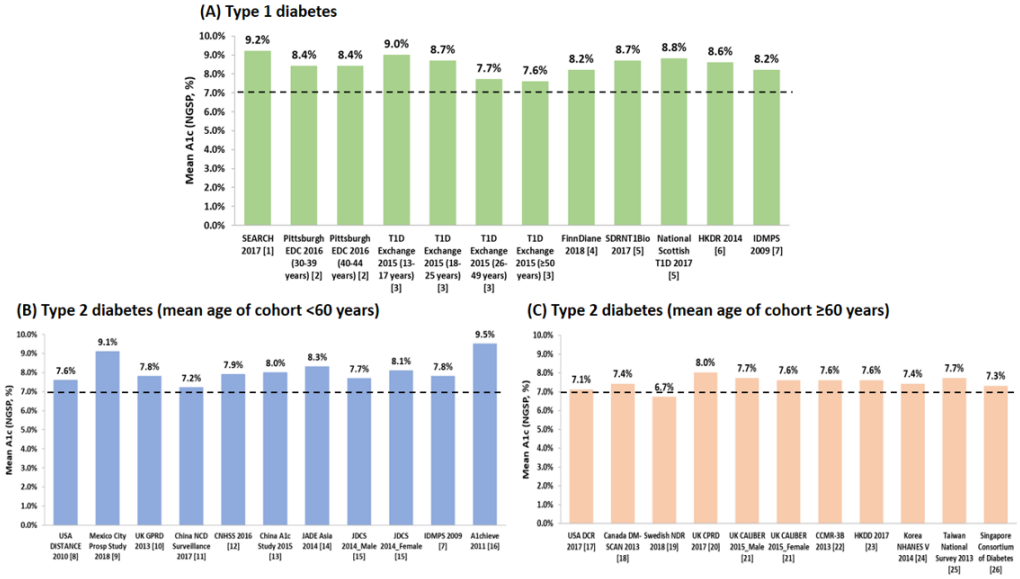
In the UKPDS, after the initial reduction of 2%, there was a progressive upward drift of $HbA_{1c}$,[261-263] in part due to ongoing glucolipotoxicity with progressive beta-cell dysfunction.[264,265] These finding have been confirmed in large-scale surveys of T2D showing loss of glycaemic control over time.[250,266] Similarly, BP tends to rise with increasing disease duration.[266] Ageing aside,[267] lack of regular monitoring, medication non-adherence and delayed treatment intensification all contribute to progressive loss of control of these risk factors in T2D in real-world practice.[268] In several surveys, fewer than 50% of patients had their treatment intensified, even though they had been suboptimally managed for more than 7 years.[269,270] On the other hand, 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.[271,272] In a meta-analysis, after an initial fall 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. The researchers estimated that an average of 23.5 hours of contact time during a 12-month follow-up period was needed to sustain a 1% (11 mmol/mol)

reduction in $HbA_{1c}$.[273,274] By re-organising care, using non-physician personnel and technology,[275] we can improve the efficiency of care delivery to address the psychosocial and informational needs of patients and improve self-care and treatment adherence, especially in those who have not yet developed complications and may have low motivation to change their habits.[276]

### *7.6 Variations in quality of care and clinical outcomes mean control of diabetes is achievable*

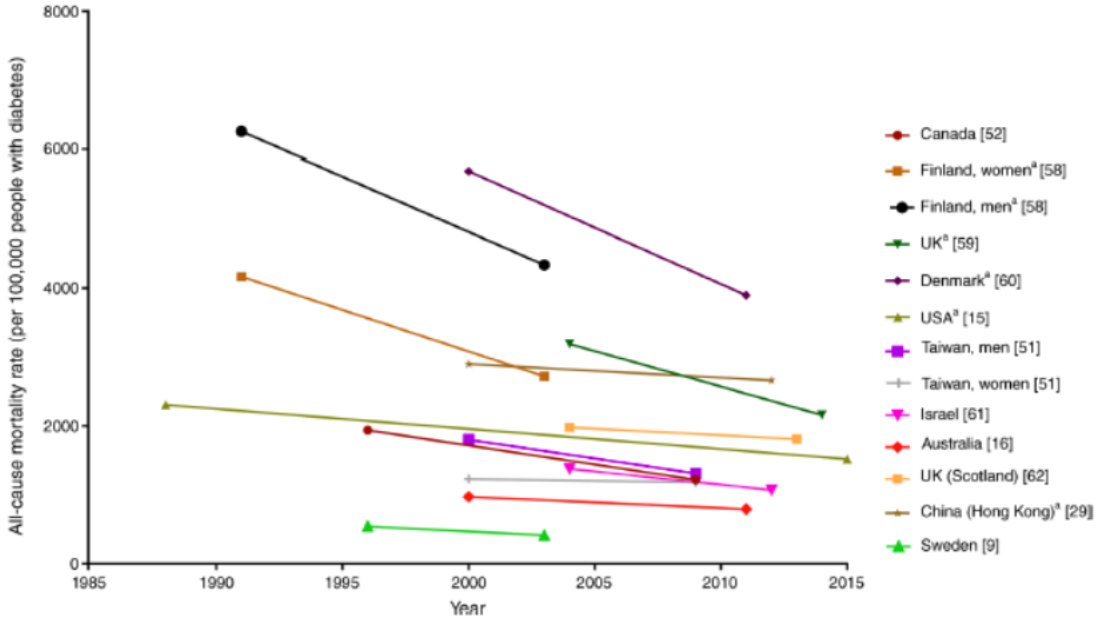
In a 12-year survey consisting of seven waves of patients with T2D, totalling 66,088 recruited by 6,099 physicians from 49 countries outside North America and Western Europe, the proportions of patients with $HbA_{1c}$<7.0% (53 mmol/mol) decreased from 36% to 30.1% between 2005 and 2017.[277] In another multicentre survey involving 10,000 patients from outside the USA and Europe, only 20–30% of people with T2D attained recommended $HbA_{1c}$ (<7.0% [53 mmol/mol]), BP (<130/80 mmHg) and LDL-cholesterol (<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 RASi, or underwent periodic eye and foot examination and blood/urine testing in accordance with international recommendations.[278] By curating data from 40 surveys consisting of 1.9 million individuals recruited from HICs and LMICs with each study enrolling at least 5,000 patients with either T1D or T2D, only 20–40% of individuals achieved $HbA_{1c}$<7% (53 mmol/mol)[247] with worse glycaemic control in patients with T1D and young patients with T2D, highlighting our failure to translate evidence to benefit the larger community (Figure 6).

**Figure 6. A global landscape of $HbA_{1c}$ in 1.9 million people with type 1 or type 2 diabetes reported in more than 20 cohorts with at least 5000 patients per cohort showing high levels of $HbA_{1c}$ especially in patients with type 1 diabetes and young-onset type 2 diabetes (refer to supplemental text for details of references).**




In HICs where access to care, education and medications are covered by either general government funding or public/private health insurance schemes, there have been notable improvements in terms of risk factors, complication rates and health services utilisation (Figure 7). In the USA, between 1990 and 2010, the declining rates of acute myocardial infarction events, death from hyperglycaemic crisis, stroke, lower extremity amputation and ESKD were 67.8%, 64.4%, 52.7%, 51.4% and 28.3%, respectively. The reduction in vascular and renal outcomes was greater in individuals with diabetes than in those without diagnosed diabetes.[19] During the same period, attainment of $HbA_{1c}$, BP, LDL-cholesterol 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 improvements in foot examination and annual serum lipid measurement, and smaller improvements in annual eye and dental examinations.[279,280]

**Figure 7. Trends in all-cause mortality among people with diabetes between 1988 and 2015, by country/region. Note these data are from HICs, showing a paucity of similar data in LMICs (Harding JL et al. Diabetologia 2018).**




In the latest analysis of the Hong Kong Diabetes Database, a territory-wide register of 338,900 Chinese patients with T2D who underwent structured assessment (eye, feet, blood and urine) every 2–3 years in publicly-funded healthcare institutions with access to education and medications, there were significant improvements in risk factor control and increased use of statins and RASi between 2002 and 2012. The proportion of patients achieving $HbA_{1c}$<7% (53 mmol/mol) increased from 32.9% to 50.0%, BP≤130/80 mmHg from 24.7% to 30.7%, LDL-cholesterol<2.6 mmol/L (100 mg/dL) from 25.8% to 38.1%. Amongst patients with diabetes for 15 or more years, the crude incidence of acute myocardial infarction decreased from 8.7 to 5.8, stroke from 13.5 to 10.1, ESKD from 25.8 to 22.5 and death from 29.0 to 26.6 per 1000-person-years between 2000–2002 and 2010–2013, respectively. 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.[266] In the latest analysis of over 770,000 adults with T2D observed between 2001 and 2016, death from all causes, CVD and cancer amongst individuals with diabetes declined by 52.3%, 72.2% and 65.1% in men, and by 53.5%, 78.5% and 59.6% in women albeit the decline was less evident in young adults between 20–44 years.[57]

There are considerable between- and within-country variations in the care cascade from awareness, diagnosis, treatment to control in both LMICs and HICs.[281] However, on average, the 2–3 fold higher and rising incidence of CVD and death rates in LMICs (e.g., India) as compared with the declining rate of CVD in North America may reflect differences in resources, capacity, access and care organisation. The close association between reduction in risk factors and clinical outcomes in both RCTs and real-world settings provides a strong business case for investing in preventive care by controlling multiple risk factors and empowering patients. This can yield high return after 10–15 years by reducing long-term complications, i.e. 'pay now, save later' rather than 'save now, pay later'.[282] In 2010, the USA spent purchasing-adjusted USD 7,383 per capita for treating diabetes, mainly for comorbidities, compared with less than USD 100 per capita in 16 low-income countries. While the USA spent 52.7% of the global expenditure on diabetes, India spent less than 1% of the world's total, despite having one of the largest populations of diabetes. Counted as a whole, all 18 countries included in the African Region defined by the IDF spent only 0.3% of the global diabetes expenditure.[160]

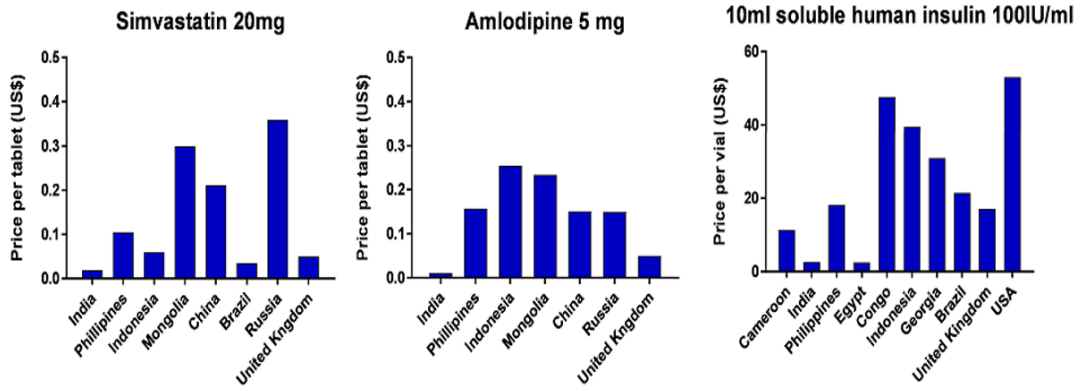
### *7.7 Importance of context-relevant data to guide local practice and policies*

Distribution of resources is often a political decision rather than based on evidence. In LMICs where local data are frequently lacking, funding bodies often have to find the right balance between investing in preventive care for future gains or providing care to patients with more immediate needs. Use of medications is core to diabetes management. Currently, most of the economic evaluations in diabetes focus on blood glucose lowering drugs and devices (e.g., insulin-based treatment regimens),[283] as well as interventions aimed at improving other aspects of risk factor control.[284] A growing number of countries allocate public funds to interventions based on cost-effectiveness,[285,286] which depends on incremental cost and health benefits often expressed as quality-adjusted life-years (QALYs). These analyses often influence reimbursement decisions for pharmaceuticals[287] and, to a lesser degree, medical devices[288] and systems of payment of HCPs.[289] Beyond treatment, there are also economic evaluations of preventive interventions targeting high-risk and specific populations,[290] as well as broader community interventions.[291]

### *7.8 Escalating costs of medications and lifelong care suggest a need to improve the efficiency in care delivery*

In the absence of country-specific and cost-effectiveness data from LMICs, economic evaluations derived from HICs[284] and international RCTs are sometimes used to guide clinical decision at a national level.[292] These analyses suggested blood glucose control using metformin, SU and insulin is cost-effective and is recommended by the WHO.[248,293] Large RCTs also confirmed that control of BP[294] and LDL-cholesterol[295] are cost-effective and (in some cases) cost-saving. With the expiry of patents, the cost of many widely-used therapies (e.g., earlier blood glucose lowering drugs, statins and angiotensin-converting enzyme inhibitors [ACEi]) has fallen markedly in recent years, making these therapies more cost-effective and affordable on a global basis. In many countries, generic drugs for treating individuals with diabetes can be purchased for just a few cents a day. Yet, surveys of drug prices have indicated wide variations across and within countries (Figure 8). These price differences, such as for insulin, are often related to the supply chain structure, mark-up by distributors, wholesalers and retailers and sometimes import duties.[296]

**Figure 8: Price differences in common medications used in patients with diabetes in countries ranked based on gross domestic product per capita in 2011. Prices of simvastatin and amlodipine are pubic sector procurement prices from various surveys conducted by WHO/Health Action International Project on Medicine Prices and Availability between 2002 and 2013. United Kingdom drug prices are based on Category M price. Insulin data are private prices based on a global snapshot on 11 May 2010 as reported by WHO/Health Action International Project on Medicine and Availability.**




World Health Organization. WHO/Health Action International Project on Medicine Prices and Availability http://www.who.int/medicines/areas/access/Medicine_Prices_and_Availability/en/WHO/Health (Accessed o 1 Jan 2018).

In areas where large variations exist in the costs between different types of therapies (e.g., classes of blood glucose lowering drugs), there is a need to assess whether the more expensive therapies provide additional benefits that justify the higher cost. In some countries, national health services and country-wide coverage schemes have enabled more effective negotiations to ensure equitable returns for

manufacturers while retaining security of supply to the consumer. Indeed, the most cost-effective strategies to control diabetes and reduce complications may change over time due purely to changes in the relative cost of therapies, which may influence future practice guidelines.

Although new technologies, including insulin analogues and insulin pumps, have the potential to improve and extend lives of people with T1D, most come at a higher cost than the interventions they replace. Globally, there is great variation in the cost of human insulin especially in LMICs.[297,298] For example, data collected by Health Action International indicates that the price a patient would have paid for a 10 mL vial of soluble human insulin ranged from USD 1.55 to USD 76.69 across different countries.[299] In a recent survey involving 13 LMICs, up to 80% of countries have access to human insulin compared with 60% for insulin analogues, with 3-fold higher price for the latter, more so in the private market. The researchers estimated that a low-income person had to work 4 and 7 days to buy 10 mL human and analogue insulin, respectively.[177] In other countries, 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 amongst manufacturers, reducing unnecessary administrative costs, promoting the use of quality-assured generic medications including biosimilars, or providing subsidy for medications with a ceiling of out-of-pocket payment through public-private partnership may make preventive care more accessible and affordable, as well as reduce the financial impact on patients and their families.[182]

While there are several strategies to promote insulin access in LMICs,[300] lessons can be learned from global efforts to tackle infectious diseases such as human immunodeficiency virus (HIV) infections, malaria and tuberculosis. In these disease areas, global funds have been established by donors to finance innovative research.[301] In the field of diabetes, patients need access to affordable ways to monitor blood glucose.[179] A prize to reward such innovations may replace traditional patent system to increase their affordability.[302] That said, these propositions can have challenging economic and moral issues including striking 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 as well as fund management.[301]

### *7.9 Close the gaps in medical coverage, care organisation and continuity*

Insufficient patient engagement and care fragmentation often lead to suboptimal control of risk factors resulting in complications which substantially increase healthcare costs.[303,304] Healthcare provision and financing are complex issues which need to be context-relevant. An analysis of the 2002−2003 World Health Survey data indicated that patients with diabetes spent considerably more than others on out-of-pocket medical expenses and had a greater chance of incurring catastrophic medical expenses.[305] Generally speaking, without adequate insurance coverage or national provision of good outpatient care which include consultations, medications and investigations, many patients are not willing to pay out-of-pocket for preventive care, often due to lack of urgency or vague symptoms, and thus, miss the opportunities of early intervention.[306] In LMICs, patients with diabetes face a much larger out-of-pocket cost than their counterparts in HICs.[307] In low-income countries, out-of-pocket cost accounted for 43% to 100% of the healthcare spending. In the USA, over 90% of patients with diabetes had healthcare insurance and their out-of-pocket payment accounted for 0–13% of the total health expenditure (Table 1). However, for some high-deductible insurance schemes or medical saving schemes, the need to co-pay may represent a barrier to seeking preventive care especially in low-income populations.[308]

In many patients with diabetes, inability to obtain adequate insurance coverage means that even patients with reasonable means may suffer huge financial loss once these complications develop.[309] A recent decision by the state of Oregon in the USA to expand its Medicaid Programme gave researchers the opportunity to evaluate the impacts of expanding insurance coverage. The results indicated that those who received insurance had a greater probability of receiving a diagnosis of diabetes and using medications for diabetes.[310] Similarly, among adults with diabetes in the USA, acquiring Medicare insurance coverage was associated with a greater increase in physician visits.[311] There is also evidence from outside the USA that insurance positively impacts on healthcare use. In Mexico, the introduction

of public health insurance (*Seguro Popular*) has led to an increase in the use of insulin and oral medications in patients with diabetes,[312] although the impact of insurance on disease control for patients with diabetes is mixed.[310]

In Japan with universal health coverage, there remain considerable variations in quality indicators including assessment for complications and risk factors, attainment of treatment targets and use of life-saving medications with better performance amongst institutions with certification.[313] In some HICs, as many as 50% of patients defaulted follow-up visits, especially amongst young and/or newly-diagnosed patients. These defaulters were more likely to have poor control of risk factors, develop complications, attend emergency departments or require hospital admissions compared with patients receiving continuing care.[314-316] In a survey including patients with T2D from HICs (Australia, France) and LMICs (Latin America), despite the marked differences in national healthcare investment, the proportion of patients receiving recommended care processes and achieving recommended treatment targets remained remarkably similar. These data suggested that healthcare investments aside, care organisation aimed at improving access and reducing default are important determinants for outcomes.[317] Here, professional training, patient education and registers are additional strategies needed to add value to care delivery with exemplary examples in both HICs and LMICs.[318]

Mandates, incentives and audits are universal pillars in healthcare reform, applicable to most healthcare systems.[319] These strategies can be used to guide payers and users to distinguish between high- and low-value services, supplemented by payment schemes to encourage the provision and subscription of value-added services.[320] In areas where both private and public sectors provide healthcare, alignment amongst payers, patients, providers and industry may allow more efficient use of emergency, inpatient and outpatient care in both sectors.[321] In Argentina, medication costs in patients with T2D were driven by long disease duration and complex therapies although good glycaemic control reduced overall cost.[322] In a multistaged quality improvement programme aimed at enhancing professional knowledge, patient self-management and access to medications in primary care setting, supplemented by registers for quality assurance, there was improvement in clinical outcomes with cost-saving.[323] In the UK, introduction of the Quality and Outcomes Framework (QOF) in primary care with financial incentives has led to improvements in both process and outcome measures.[324] In Asia, several governments including China, Taiwan, Hong Kong, Singapore have adopted a data-driven strategy by providing or subsidising structured risk assessment, education and management programmes.[325,326]

## 8 Interventions directed at population-wide and at high-risk individuals for prevention of T2D

Given the lifecourse and multidimensional nature of diabetes including environment and lifestyle factors, a multipronged, multitiered and multisectoral strategy is essential to prevent and manage diabetes. This could include, but is not limited to, the use of fiscal measures to protect the environment with better city planning, control of emission of air/water pollutants, regulation of food safety and quality, introduction of sugar-tax, designation of tobacco-free public areas and creation of healthy cities with more 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 education through provision of secondary school education and increasing health education in early school curriculum, may improve health literacy and help raise disease awareness. Finally, better maternal and child health will play important roles in the lifecourse prevention of diabetes, although more research is needed to identify high-risk mothers and children for more targeted interventions.[327]

The societal measures aimed at improving the wider determinants of health-related behaviours are in accordance with the United Nations Sustainable Developmental Goals, where quality education, environmental and social protection along with an appropriately functioning healthcare system are key to a sustainable economy. Practitioners, researchers and managers, who have expert knowledge in the multidimensional nature of diabetes as well as 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 policymakers, corporations and civic community. These concerted actions are needed for designing,

implementing and evaluating a context-relevant and integrated society-community-individual strategy aimed at changing the ecosystem, improving the healthcare environment and ensuring healthcare equity for preventing and controlling obesity, diabetes and other NCDs.[328]

### *8.1 Preventing T2D can prevent CVD – challenges and opportunities*

Several RCTs and meta-analyses have confirmed that T2D can be prevented by lifestyle interventions in closely-supervised situations.[329-333] In China, lifestyle intervention in middle-aged men with IGT reduced conversion to T2D by 40% at 6 years. After the study was completed, the intervention group continued to benefit with 20% risk reduction for retinopathy, CVD and all-cause death 30 years after the trial commenced.[256] The benefits of lifestyle interventions with or without medications including metformin, alpha-glucosidase inhibitors and thiazolidinediones in reducing onset of T2D in individuals with IGT and multiple cardiometabolic risk factors have also been reported in studies conducted in the USA, Europe, India and Japan. Similarly, lifestyle interventions also reduced hypertension in individuals without IGT.[334,335] This evidence has led to the establishment of systematic, high-risk individual-level T2D prevention programmes in HICs such as Germany, Finland, the USA, the UK, Poland and Singapore. Real-world implementation of these lifestyle intervention programmes with less intensity has yielded favourable results in countries from Asia, Africa and the Middle East (Table 3).

Translating evidence to practice should consider both the absolute risk of future T2D in that individual, as well as the risk reduction that can be achieved by the intervention. These parameters form the basis of the absolute risk reduction (ARR, difference between the event rates in the control and experimental group), and the number needed to treat (NNT, inverse of ARR). Thus, for the same risk reduction, high-risk individuals will gain more from the intervention with lower NNT to achieve positive outcomes. Countries that have translated this evidence often adopt an integrated approach of establishing guidelines, training an effective workforce of non-physician lifestyle coaches along with various types of HCPs, monitoring quality through simple registers, encouraging reimbursement, raising awareness and marketing the programmes.[336,337] To date, the evaluation of the National Diabetes Prevention Programme in the USA has demonstrated rapid increase in trained lifestyle coaches and participation, as well as favourable weight loss of 4% at one year that is generally in line with the magnitude of weight loss observed in community translation trials.[336,337] This programme has also achieved healthcare 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.[338]

Compared with research settings often confounded by volunteer bias and close supervision, the uptake of the screening and intervention programmes and intensity of intervention in real-world practice is often not as high.[339] In the USA, the MOVE–IT (MOtiVational interviewing InTervention) trial 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 CVD identified during routine health checks.[340] 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 fraction of the population for whom the intervention was designed. Other barriers in implementing primary prevention programme include economic constraints, insufficient resources, cultural taboos, poor health-seeking behaviour and lack of knowledge and skills.[341] To this end, some researchers used behavioural economics such as giving financial incentives to increase physical activity, using visual cues to encourage selection of heathy food choices or losing deposits for not reaching targets in a contract of weight reduction.[342] These studies have yielded encouraging results, suggesting similar approaches can be further explored.

A critical 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. Common methods that have been employed include word of mouth, information through flyers and posters, advertisement, recruitment through existing programmes, conducting community screening programmes, recruiting selective populations (e.g., using risk scores), as well as targeting family members of patients with diabetes and staff of corporations. There are few studies that examine the most effective approaches to identify high-risk individuals relevant to the local population and healthcare setting. It is also unknown

whether approaches that work in developed countries, with generally high literacy and well-supported primary care system, are translatable to other settings where illiteracy and availability or access to primary care are important barriers. These challenges have fuelled a new wave of research into the science of engagement and uptake, as well as tailored modalities of delivery to optimise participation and effectiveness. In a recent meta-analysis of real-world T2D prevention programmes, group intervention using community health workers or professionals were similarly effective with weight loss as the major determinant, the latter being closely associated with levels of engagement.[343] Thus, by developing and evaluating innovative multicomponent care models, including but not limited to, technology and trained community health workers/peers with linkage to healthcare system, these challenges are not insurmountable.

### *8.2 Use of technology and non-physician personnel may enhance the cost-effectiveness of lifestyle interventions*

In a systematic analysis of 28 studies, the economics of lifestyle intervention programmes conducted mainly in HICs, consisting of at least 2 sessions in 3 months delivered to people at increased risk of developing diabetes was analysed using cost expressed in USD in 2013. The median programme cost per participant was USD 653 with lower costs for group- (USD 417) and community/primary care-based programmes (USD 424). This is compared with USD 5,881 for the DPP (Diabetes Prevention Program) trial and the DPP Outcomes Study (DPPOS). From a health system perspective, the median incremental cost-effectiveness ratios (ICER) was USD 13,761 per QALY saved. Group-based programmes were more cost-effective (USD 1,819 per QALY) than individual-based programmes (USD 15,846 per QALY).[344] More recently, in a 15-year analysis of the DPP/DPPOS which also included a metformin intervention arm, metformin was found to be cost-saving in preventing diabetes with reduced long-term complications, especially amongst those with obesity, high fasting plasma glucose or a history of gestational diabetes.[345]

As a general rule, interventions are more cost-effective when the intervention is targeted at individuals who are at a high absolute risk of T2D,[346] and when the interventions are delivered in a group format by trained community health workers/peers. The advent of mobile health (mHealth) programmes offers an opportunity for developing potentially scalable and cost-effective prevention management strategies for diabetes and other NCDs especially in LMICs.[347] In India, a short message service (SMS) study using mobile phones to provide health behaviour messages to men with IGT found a 36% relative risk reduction in the development of T2D after two years.[348] 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 T2D. It is expected that the trained personnel will disseminate knowledge to the local community by organising awareness programmes. Similarly, promising internet- and social media-based approaches to supporting lifestyle changes are underway, but data on the long-term outcomes of these programmes from RCTs are not available.[349]

In a multicentre study conducted in South America, a 12-month mobile phone-based health intervention using monthly motivational counselling calls and weekly personalised text messages resulted in meaningful reduction in BP and body weight which was sustained after 6 years, especially amongst those who received at least 50% of the calls.[350,351] Indeed, the use of information and communication technology (ICT) such as wearable devices to monitor physical activity, sleep pattern, pulse rate, BP and blood glucose, along with mobile applications (APP) 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, encourage behavioural changes such as improving healthy dietary habits, encouraging physical activity and losing weight.[352]

Although these results support the potential of using digital health solutions to increase the reach and impact of lifestyle intervention and weight management programmes, healthcare workers and professionals are often needed to improve engagement, suggesting that a 'high tech, soft touch' approach may address the psychosocial and informational needs of these individuals.[343] Similar to drug

development, there are investment costs for developing, marketing and maintaining these technologies with return of investment as a key consideration. Thus, until there are high levels of evidence, supported by cost-effectiveness analysis, sustainable engagement and willingness-to-pay are major challenges in the scaling up of these prevention programmes.

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

In RCT setting, individual-level lifestyle intervention aimed at changing obesity, diet and physical activity has generally had a similar impact in all populations and in all ethnic subgroups within populations.[353] However, these observations may be obscured by the dominance of participants from HICs. Compared with Caucasians, Asians have lower acute insulin response for the same decrement in insulin sensitivity.[109,354] In these populations, a small increase in adiposity, especially if central, can worsen insulin resistance and decompensate beta-cell function. While weight reduction in these high-risk individuals may reduce risk of diabetes, alternative strategies targeted at ameliorating glucotoxicity to preserve beta-cell function, especially in lean individuals with glucose intolerance needs further exploration.[89] Approximately half of all individuals in T2D prevention RCTs are from Europe and the USA. The other half are from India, China and Japan. Without representative data from other regions, it is difficult to extend the cost-effectiveness of T2D prevention interventions from HICs to LMICs where data are scarce.[290] Besides, given the lack of information of other population-based risk factors and population attributable risk due to societal determinants, notably poverty and education,[151] maternal nutrition, early-life stunting,[355] infections of various kinds,[356] dietary factors and environmental factors such as pollutants which are highly prevalent in LMICs (Table 2),[357] the cost-effectiveness of these lifestyle intervention programmes remain uncertain.

### *8.4 From effectiveness to efficiency of T2D detection and prevention programmes*

Nearly all T2D prevention trials have focused on interventions in individuals with IGT. However, in real-world practice, the 75-gram OGTT is rarely used to detect abnormal glucose tolerance (i.e., impaired fasting glucose [IFG] and/or IGT) and few individuals have measurement of 2-hour post-challenge glucose levels, needed to diagnose IGT. Although there is epidemiological evidence suggesting that $HbA_{1c}$ predicts incident diabetes and CVD in a non-diabetic population in a linear manner,[358,359] there is very limited evidence regarding the benefits of T2D prevention programmes among those with isolated IFG or with isolated, elevated $HbA_{1c}$.[360] There are also knowledge gaps regarding the effects of haemoglobin variants[361] and thresholds for haemoglobin glycation which can influence the diagnostic values of $HbA_{1c}$ in different ethnic groups.[362,363]

Additionally, hyperglycaemia *per se*, regardless of the definition used, may not be the best way to target high-risk individuals while its combination with other information into a risk score is more robust in predicting risk for diabetes.[364] These risk factors can be based on questionnaire (e.g., family history of diabetes, use of tobacco, history of maternal hyperglycaemia, hypertension, high blood cholesterol, non-alcoholic fatty liver disease (NAFLD) and/or polycystic ovary syndrome) and self-measurement (BP, BMI, waist circumference) for incorporation into various risk scores to detect high-risk individuals for intervention. There are now many published risk scores which require validation and calibration when applied to a different population.[365] These unanswered questions aimed at identifying individuals who will benefit most from lifestyle intervention requires further research and evaluation in order to assist decision-makers in delivering the intervention in the most efficient and cost-effective manner.

Pharmacotherapy, such as low cost metformin, may have a place either as an alternative or as an adjunct intervention.[345] However, pharmacological T2D prevention implies that an individual will receive a diagnosis and glucose lowering therapy and attend a physician regularly for monitoring. Given the large number of people at risk, intervention using medications such as metformin which is at best effective only in 10-15% of people with IGT, and medical procedures, should not be considered without a high level of certainty. That said, given the effectiveness of lifestyle intervention and metformin, in individuals at high risk of conversion or in those with practical difficulties in adhering to structured

lifestyle intervention, a combination of metformin and lifestyle intervention, or early-stage metformin as an alternative to lifestyle intervention are options worth exploring.

One of the limitations in these trials is the proxy endpoints since the goal of T2D prevention is not solely to reduce the incidence of T2D, but also to reduce its clinical complications.[366,367] Since CVD is the leading cause of death in diabetes or abnormal glucose regulation, there is also strong argument of using a polypill-based strategy. The latter contains a fixed-dose of several inexpensive medications such as metformin, statins and RASi, which may prevent both T2D and CVD and should be a key priority for governments and/or other sponsors including pharmaceutical industry.[368] Several RCTs have demonstrated the effectiveness of using polypills to improve the control of multiple risk factors including BP and lipids in both HICs and LMICs.[369-371] In a 5-year RCT conducted in Iran involving middle-aged individuals with CVD and/or cardiometabolic risk factors, treatment with a four-in-one-pill (hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg and enalapril 5 mg) reduced CVD by 20-40%, depending on prior history of CVD, with overall good safety and adherence.[372]

### *8.5 Short- and long-term impact of primary prevention of T2D on healthcare utilisation*

The decision to introduce systematic screening for undiagnosed diabetes in many settings has been guided by the WHO criteria for screening programmes.[373-375] 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 about three years. Based on data from the ADDITION-Europe cohort, researchers simulated models which indicated that screening followed by multifactorial management resulted in 3.3% ARR and 29% relative risk reduction (RRR) at 3-year and 4.9% ARR and 38% RRR at 6-year for CVD.[376] Although long-term observational data from the ADDITION cohort has yet to confirm the benefits of screening on CVD or all-cause mortality,[377] recent health economic analysis from Denmark suggests lower healthcare costs in the screened-group compared with the non-screened group, with the screening programme being cost-saving amongst those who were screened positive.[378] A mathematical modelling exercise has suggested that in the US population, screening for T2D would be cost-effective when started between the ages of 30 years and 45 years with screening repeated every 3-5 years.[379]

Most experts recommend a screening strategy targeted at high-risk individuals with aforementioned risk factors and risk markers such as obesity and high BP which can be self-assessed. These data can be used to compute risk scores to detect high-risk individuals followed by confirmatory laboratory tests including 75-gram OGTT and/or $HbA_{1c}$.[365] Pending evidence regarding the best screening strategy, systematic reviews including economic analysis suggest that promoting healthy diet and physical activity especially if delivered in groups or in primary care setting, targeting high-risk individuals can be cost-effective in both HICs and LMICs.[343,344,380]

In LMICs with the least affordability to pay for expensive, late-stage complications, there appear to be strong economic argument to screen for high-risk individuals for lifestyle intervention. However, this strategy will undoubtedly lead to identification of a large number of individuals with previously undiagnosed diabetes, which can be as high as 70% in some LMICs.[381] In a nationwide screening programme conducted in Brazil, individuals aged 40 years or above were invited to undergo capillary blood glucose testing at primary healthcare centres through mass media and awareness campaign. Individuals with positive test were recalled to undergo confirmatory test using fasting plasma glucose. The programme aimed at detecting undiagnosed diabetes and building capacity of primary care teams. Amongst 22,069,905 screening tests performed, 3,417,106 (15.5%) were screened positive. Amongst them, 10% (n=346,168) were confirmed as new cases with 92.2% (n=319,157) being incorporated into the healthcare system.[382]

The uncovering of this large population of individuals with undiagnosed diabetes who need continuing care, assessment, education and medications have huge resource implications, which may compromise the care received by those diagnosed through standard clinical channels, as well as compete for the resources needed for primary prevention using lifestyle intervention. Even for programmes aimed at

detecting and treating HIV infections, supported by philanthropic funds, there are still persistent gaps in achieving targets.[383]Thus, the implementation of large-scale and resource-efficient T2D prevention programmes, targeting high-risk individuals and detecting/treating undiagnosed diabetes should be supported by a prepared healthcare system.[384,385] In LMICs, this will necessitate upfront investments in building infrastructures and capacity.[386] To maximise the use of finite resources, inter-sectoral collaborations and public-private partnership are needed to develop an integrated system using physicians and non-physician personnel to cover 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 T2D epidemic, tailored according to each country's particular environmental and political contexts.

### *8.6 Population and individual-level prevention – getting the right balance and how to evaluate*

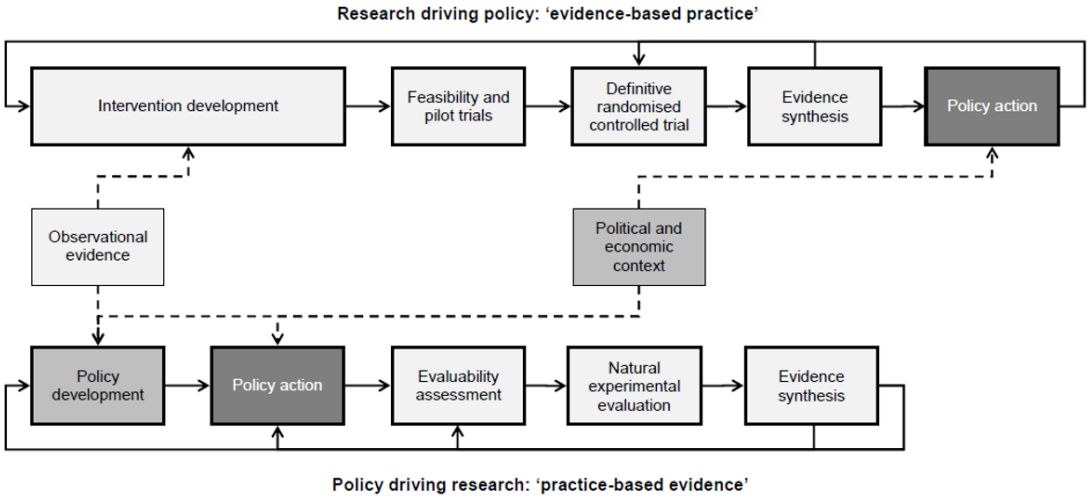
The risk factors that are the targets of effective individual-level interventions (e.g., lifestyle intervention) should also be targets for population-level interventions,[387] although adoption of a population approach calls for better understanding of the key determinants of the environmental and behavioural drivers of T2D risk, relevant to the area concerned. Physical activity, dietary behaviour and obesity levels are often seen as an individual's decisions or preference. However, these behaviours and social norms are driven principally by more upstream societal-level factors such as the overall food supply, price, marketing, the sedentary nature of most modern occupations, the lack of availability of health-promoting transport options and the structure of the built environment. Seen from this perspective, the emergence of T2D is predominantly a societal problem for which societal-level solutions are also required.[388]

Table 2 summarises a range of social, developmental, environmental and behavioural risk factors for which the evidence of association and population attributable risk is less clear. The extent to which these risk factors could be modifiable and could 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 where interventions are developed, usually using RCT design, and tested in multiple populations and settings. Once the intervention is found effective, this is followed by meta-analyses and systematic reviews of similar results which will contribute to the formulation of evidence-informed practice guidelines and public policies, as in the case for diabetes management and T2D prevention in high-risk individuals.[389]

There are a few examples of population-level interventions where researchers used RCTs to demonstrate the effects of using salt substitution to reduce blood pressure[390] and that of using housing vouchers and counselling to encourage women and their children to move out from a high poverty to a low poverty areas with reduced prevalence of extreme obesity and diabetes.[391] Although this reductionist RCT approach follows the classical teaching, given the threat posed by T2D, bold policy-level action followed by evaluation using a range of quasi-experimental methods is an alternative approach (Figure 9).[392] In this fundamentally different approach, the best available observational evidence is used to support a policy-level intervention which is then evaluated in the real-world using quasi-experimental methods. Measures to cut tobacco use[393] to reduce deaths, and mandatory seat belt use to reduce road traffic injury have followed this approach.[394]

In Scotland, a policy intervention which 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 impact on ischaemic heart disease. Compared with the number of admissions due to acute coronary syndrome in the 10-month period prior to the passing of the legislation, there was a 17% reduction during the same period in the following year after its enactment.[395] When similar interventions have been implemented elsewhere, evidence synthesis of the effectiveness of tobacco control strategy was then possible using meta-analysis.[396] Given the multidimensional nature of diabetes, multiple societal-level interventions will be required, albeit each of which may only have a small effect. For example, policies to implement sugar-sweetened beverage taxes and levies are increasingly being evaluated[397] but such evaluations are usually focused on proximal outcomes like purchasing or consumption. In this type of policy intervention, more distant outcomes such as incidence of T2D, have to be modelled rather than directly observed.[398]

**Figure 9. Routes to the translation of evidence into action in clinical and public health interventions (Ogilvie D et al SocArXiv 2019).**




### *8.7 Primary prevention of T2D requires bold evidence-informed political actions*

In recognition of the lifecourse nature of diabetes and other NCDs, members of the Commission reiterate the importance of using educational policy at all levels, including 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. We also emphasise the importance of using environmental policies to build healthy cities through inter-sectoral 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 T2D, we also re-affirm the importance of tobacco control as an important policy in the prevention of T2D and its complications. These societal strategies are accord with the 'best buys' from the WHO[327,393] and the recommendations by the United Nations Sustainable Developmental Goals.[399]

Within this framework, members of the Commission further proposed a series of possible actions which could be undertaken by governments and policymakers at the supranational, national, regional and local levels to influence those risk factors (Table 3). The approach used in any given setting will be determined not only by epidemiological considerations of expected benefit but by considerations of political feasibility. The cost-effectiveness of some of these population-level interventions have been evaluated, including sugar-sweetened beverage taxes,[400] restrictions on unhealthy food advertising,[401] mass media campaigns to promote healthy lifestyle[402] and economic incentives to increase fruit and vegetable consumption.[403,404]

Since the effectiveness of such interventions cannot be determined from RCTs, simulation modelling is often used to estimate their cost-effectiveness. The evidence from the few studies available suggests that these interventions are generally cost-saving or cost-effective.[405] 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. As they are relatively inexpensive, these interventions 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. As estimates of both cost and effectiveness of population-wide interventions have been modelled-up from numerous assumptions, rigorous natural experiments are needed to evaluate effectiveness and help prioritisation and implementation of such approaches.

Decisions to allocate resources for screening, prevention and treatment are often context-relevant taking into consideration local cultures, socioeconomic development and existing capacity of healthcare

systems. That said, given the life-threatening nature of untreated or poorly-managed diabetes, it is important that all healthcare settings act promptly to provide care meeting minimal standards to all individuals diagnosed with diabetes. Amongst those who are in contact with the healthcare setting and have a high likelihood of having prevalent but undiagnosed diabetes, they should have a diagnostic test, and if positive, be included into the same system of care as those people with known diabetes. The implementation of more systematic approaches to find individuals with undiagnosed diabetes and those at high-risk of future diabetes is a contextual healthcare policy decision, influenced by the structure of individual healthcare systems.

### *8.8 An example to illustrate priority actions in HICs versus LMICs*

Depending on the environmental, political and social context, the policymakers will need to adopt a multicomponent strategy to combine population-wide and individual-level interventions aimed at high-risk individuals. Most literature suggests that obesity, physical inactivity and different dietary and nutritional factors are amongst the most modifiable risk factors, which form the basis for many of the individual-level primary prevention programmes. Using the USA as an example, the population attributable risk due to obesity, poor diet and physical inactivity was 87% amongst women, suggesting that the overwhelming majority of cases of T2D could be averted if women could adopt a healthy diet, by being physically active and not obese.[406] However, the dominance of Western populations in the literature on risk factors and T2D risk (Table 2) and the lack of data from Asian and African populations raise the question whether estimates of population attributable risk could well differ between populations. It is here that local data regarding the population attributable risk due to risk factors such as access to healthy food choices, food insecurity, nutrition, sleep pattern, physical activity and psychosocial stress taking into consideration demographic, environmental and socioeconomic determinants become important for prioritising actions.

The balance between high-risk individual-level prevention and societal approaches to prevention may differ between countries and may also differ within a country over time. Countries should take into consideration the scale of the diabetes problem in their own populations and the ratio of diagnosed to undiagnosed cases, the capacity of primary healthcare systems to undertake screening for undiagnosed diabetes and hyperglycaemia, the capacity for the system to care adequately for additional cases and to provide systematic preventive interventions to those at risk.

As an example, Table 5 compares characteristics of England and Jamaica. 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. There is a strong and well-funded primary healthcare system with the majority of individuals 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 T2D screening and lifestyle intervention programme which will complement population-wide prevention strategies.

In Jamaica, by contrast, funding is far lower and many individuals with diabetes do not even have access to complication screening or risk factor control. In this resource-poor context, a change in the healthcare system to improve diabetes care for the existing population is a priority.[407] Although it might seem intuitive to encourage investment in screening for high-risk individuals for individual-level intervention, this would risk destabilising an already stretched healthcare system. Given the scale of the problem, in addition to improving care standards and health knowledge using non-physician personnel and ensuring access to essential medications, it may be preferable to give even greater priority to interventions aimed at shifting risk factors in the whole population. Caribbean countries have, for example, taxed sugar and are implementing other fiscal measures. This contrast between England and Jamaica illustrates the need for countries to consider a range of epidemiological, economic and healthcare system factors in determining the appropriate balance in any individual country between investments in improving the healthcare of individuals who have diabetes now, interventions in those who will get it soon and more upstream changes that have the potential to influence risk in future generations.

### *8.9 A global epidemic requires local solutions through collective efforts*

We are living in a rapidly changing world where globalisation and technological advancement have increased life expectancy in many parts of the world. These forces have created big changes in 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 subject to external and peer influence, these societal changes have transformed our perspectives, expectations and behaviours leading to new social norms, notably our lifestyles associated with city-dwelling. Rapid rural-urban migration has led to progressive widening of social disparities and increasing income inequality, in part 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 is a wake-up call to the global community on how patients with diabetes and NCDs, especially those with poor access to care and social deprivation, were disproportionately affected during these emergencies. The large number of people affected overwhelmed the healthcare system, even in HICs, with enormous human suffering and economic repercussions.[408-411] In this light, most healthcare systems in LMICs are traditionally designed to treat acute injuries and communicable disease. Not only are these low-resource systems unable to cope with these global emergencies, they are also ill-prepared to manage this growing number of individuals with diabetes and their long-term complications. The rudimentary primary care systems and insufficient experience, skills and exposures for most HCPs against a backdrop of rapid knowledge and technological advancement in the field of diabetes and other NCDs, mean many individuals are not diagnosed, treated or controlled in a timely manner.

Even in affluent areas, decades of social and medical care consumed by this growing population is having an enormous toll on their well-resourced healthcare systems. Many decision-makers have little information to plan resource allocation in order to design, develop and sustain a high-quality integrated diabetes prevention and care service for long-term benefits. The sheer number of individuals with or at risk of diabetes also deter many payers including insurers, governments and corporates to invest and opt for status quo,[412] despite the cost-effective or cost-saving nature of these T2D prevention and care programmes.[413] Improving care aside, strong political will and inter-sectoral collaborations are needed to tackle many of these societal determinants, notably environment, education and poverty, closely linked with diabetes.

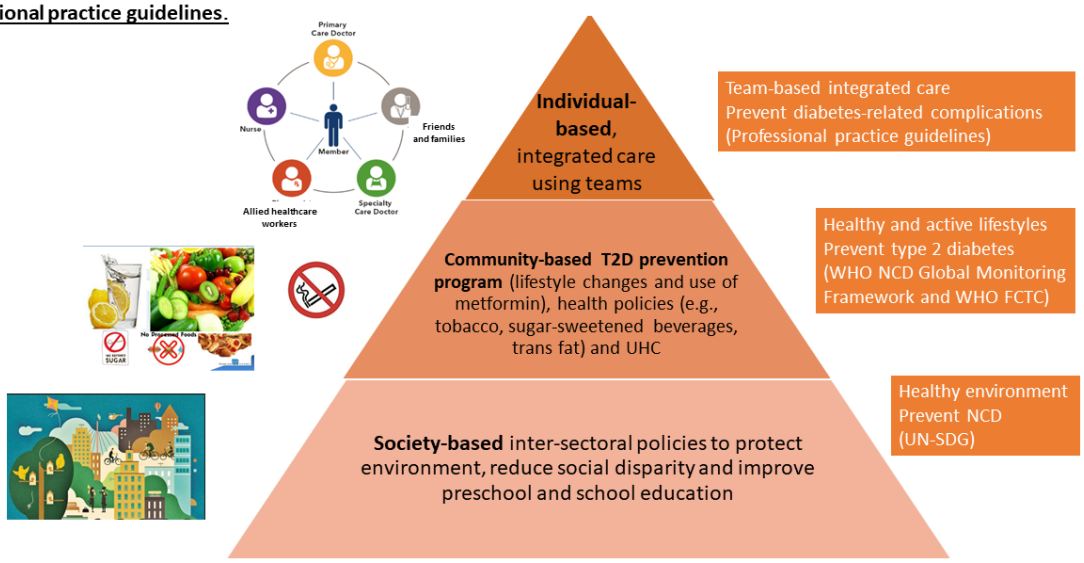
### *8.10 An integrated society-community-individual strategy to reduce burden of diabetes and other NCDs*

Given the multidimensional nature of diabetes, it follows that a multidimensional solution is needed to create short-, mid- 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. Once diabetes develops, care fragmentation and insufficient patient engagement can worsen control of multiple risk factors leading to multiple morbidities. Due to the silent nature of diabetes, phenotypic heterogeneity and pluralistic needs, we argue strongly for the need to redesign the practice environment, team structure and workflow in order to gather data systematically, stratify risk, personalise care, provide feedback and perform periodic monitoring. By establishing community-based diabetes teams/centres and building a strong primary healthcare system with linkage to the hospital-based healthcare system, trained diabetes teams will be in a prime position to identify high-risk individuals for lifestyle intervention including the use of metformin and other medications (e.g., polypill) to prevent T2D and CVD.

This individualised approach needs to be complemented by policies that support building smoke-free, healthy cities aimed at reducing environmental pollutions, ensuring food security, increasing affordability of healthy foods, promoting healthy eating (e.g., nutritional labelling, school meals), encouraging physical activity (e.g., walking paths, sports) and avoidance of harmful substances (e.g., tobacco, sugar-sweetened beverages, trans fat) using taxation and warning labels.[414] To reduce the long-term burden of diabetes and other NCDs, we need to use inter-sectoral polices to improve the ecosystem,

protect the environment and reduce social disparities. Apart from promoting universal health coverage, providing education starting from preschool up to at least secondary levels will help improve literacy closely linked to better health awareness and disease prevention (Figure 10).

**Figure 10. A conceptual framework for a multicomponent society-community-individual strategy to integrate primary and secondary prevention supported by health and inter-sectoral policies including universal health coverage (UHC), preschool/school education and social/environment protection in line with the United Nations Sustainable Developmental Goals (UN- SDG), WHO NCD Global Monitoring Framework, WHO Framework Convention for Tobacco Control (FCTC) and professional practice guidelines.**




## 9 Interventions directed at patients with diabetes and the healthcare systems

The inter-ethnic differences in clinical outcomes, such as high rates of diabetic kidney disease reported in non-Caucasians compared with Caucasian population in epidemiological surveys[415] were considerably attenuated in RCT settings where access to care and support is more assured and structured.[216,416] Compared with the younger and newly-diagnosed patients in the UKPDS conducted in the pre-statin and pre-RASi era,[262,263] participants with either CVD or multiple risk factors in landmark studies including the ACCORD,[229] VADT[230] and ADVANCE trials[231] had 50% lower incidence of CVD and death. In the Steno-2 Study[417,418] and J-DOIT3 Study where patients received intensive treatment to control multiple risk factors, there were marked reductions in cardiovascular-renal events and death rates.

As an example, the J-DOIT3 Study recruited 2,280 middle-aged Japanese patients, of whom 11% had prior CVD. Patients randomised to the intensive treatment group were informed of their treatment targets and given equipment to monitor their BP and blood glucose at home with access to nurse education, whilst their attending physicians were asked to reduce their risk factors within 6 months. This multicomponent strategy had led to extremely low events with no ESKD events and less than 100 CVD events at 8 years. These examples demonstrated how the delivery of structured and continuing care using a team approach with regular monitoring and access to life-saving medications such as statins and RASi can lead to dramatic reduction in clinical events and death rates as compared with that observed in usual care settings.[419,420]

### *9.1 Close knowledge gaps in patient-important outcomes to improve psychological health and behaviours*

Although RCTs and meta-analyses[208,210,211] have confirmed the benefits of reducing multiple risk factors in improving clinical outcomes, the volunteer bias of participants and investigators as well as the artificial nature of the trial settings, pose major challenges in translation in part due to poor access, affordability and adherence. Few RCTs reported patient-important outcomes such as quality of life, treatment costs (direct/indirect) and use of hospitalisation resources as primary outcomes.[421] Compared

with the large number of RCTs evaluating technologies, few research studies examined the socio-economical-cultural factors which underlie behavioural changes in order to achieve 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, the lack of consideration of patient's socio-personal context, personal values and preferences have reduced their relevance and effective implementation especially in LMICs or low-resource settings.[422,423] In some vulnerable populations due to social inequalities or cultural barriers, using outreach programmes or community-based centres may improve access to care compared with traditional clinic- or hospital-based settings. Similarly, using trained non-physician personnel (e.g., trained community health workers/peers) to empower and support these individuals (and their families) to manage stress and solve problems during their day-to-day living with diabetes may enhance their resilience in self-management.[424]

In order to translate these efficacy data in trial settings to cost-effectiveness data in real-world practice, we need to develop frameworks where environment, care settings, providers, processes, supporting systems and payers are aligned in order to create impacts.[425] To close these knowledge gaps, investment is required to fund new research methods and studies conducted in real-world setting with publications of these results in leading academic journals in order to create a paradigm shift focusing on implementation and evaluation in real-world setting.[426]

### *9.2 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 United Nations Sustainable Developmental Goals 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 in order to achieve positive outcomes. Using the physician per inhabitant ratio as an index of capacity, the figures in 2018 ranged from 5.0 per 1,000 in Cuba, 3.9 per 1,000 in Argentina to 0.02 per 1,000 in Malawi. In the top three countries with the largest number of individuals with diabetes, the figures were 1.5 per 1,000 in China, 0.6 per 1,000 in India and 2.3 per 1,000 in the USA. In Europe, the figures were 2.85 per 1,000 in the UK, 3.17 per 1,000 in France and 3.99 per 1,000 in Italy. Even in countries/areas with ratios higher than the recommended ratio of 1.9 per 1,000 by the WHO,[427] there is a need to train non-physician personnel to assist physicians to provide continuing care of these individuals with multiple needs.

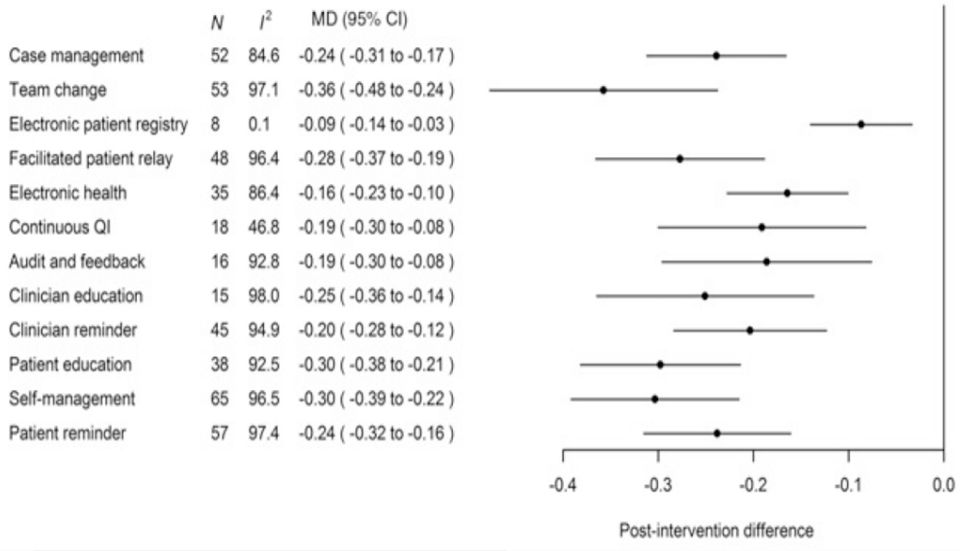
During the life journey of an individual with diabetes, he/she may need professional advice from specialists, family doctors, allied healthcare workers (e.g., nurses, dietitians, social workers, pharmacists). Apart from friends and families, these individuals may need, but frequently do not have continuing support from trained community health workers/peers with well-delineated roles, in order to cope with the day-to-day challenges posed by self-management.[428] In many LMICs, knowledge transfer from skilled workers to community health workers and trained peers may be the only way to meet the huge service demands, pending healthcare reforms and capacity building. In the 'Step by Step Foot Project' piloted and carried out in India and Tanzania, education of both HCPs and patients about proper limb care are used to reduce amputation.[429]

While we emphasise the use of non-physician personnel to make diabetes care more accessible and sustainable, given the large number of patients requiring diabetes care with different levels of complexity and shortage of HCPs with special knowledge in the field, especially in LMICs, policymakers, payers and planners are urged to increase investment and develop diabetes as a specialty in order to improve care standards, provide training and conduct research for informing practices and policies. Apart from building infrastructures, there is an urgent need to advance career paths of HCPs with appropriate knowledge and skills in order to reorganise care, develop teams, provide on-job training and teach undergraduate students in order to close the gaps in professional knowledge as a prerequisite to delivering high-quality diabetes care.[430,431]

### *9.3 Use 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 impacts of quality improvement. By promoting quality improvement as a science, HCPs, planners, managers, payers, researchers and users of the system, i.e., people with the conditions, can collectively design systems, train staff and develop protocols to improve the quality of care with ongoing data collection to identify care gaps and evaluate effectiveness.[432] In Mexico, implementation of a comprehensive programme to define risk profiles, individualise care and empower patients resulted in significant improvement in attainment of $HbA_{1c}$ target and negative emotions, although the proportion of patients who persisted with the programme at 12 and 24 months declined by more than 50% and 75%, respectively.[433] In a meta-analysis of multicomponent quality improvement strategies targeting systems, patients and HCPs for 12 months or more, task shifting, patient education/self-management support and facilitated relay (using nurses, healthcare assistants [HCA], trained community health workers/peers, information technologies) to improve patient-provider communication have the largest effect sizes in reducing $HbA_{1c}$ (Figure 11) with similar improvements for BP and LDL-cholesterol.[275] 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.[323,434,435]

**Figure 11. A meta–analysis of 181 trials showing the effects of different quality improvement strategies targeted at patients, providers and systems on $HbA_{1c}$ (NGSP %) in patients with type 2 diabetes (n=135,112) receiving multicomponent integrated care versus usual care. Team change, facilitated patient relay and patient education/self management have the largest effect size, expressed as mean difference (MD) with 95% confidence interval (CI). Similar changes are also reported for blood pressure and LDL-cholesterol. *N* is the number of trials (Lim LL et al Diabetes Care 2018).**




### *9.4 Change workflow and set up Diabetes Registers to deliver data-driven care*

As far back as 1990s, the IDF-Europe and WHO-Europe launched the St. Vincent's Declaration proposing structured data collection to detect microvascular complications (notably retinopathy and neuropathy) and improve care standard in people with T1D. This was soon followed by a similar initiative in Latin America (Diabetes Declaration of the Americas [DOTA]) where a standardised form was adopted by many countries in the region to establish registers (Qualidiab).[436] These initiatives provide useful learning on how to use data from these registers to identify care gaps and monitor outcomes.[437] Many of these T1D registers, such as the Pittsburgh Diabetes Register in the USA established in the early 1980s, have informed the world about the marked variations in terms of incidence and care standards, as well as the secular trends of complications (Figure 5A).[438]

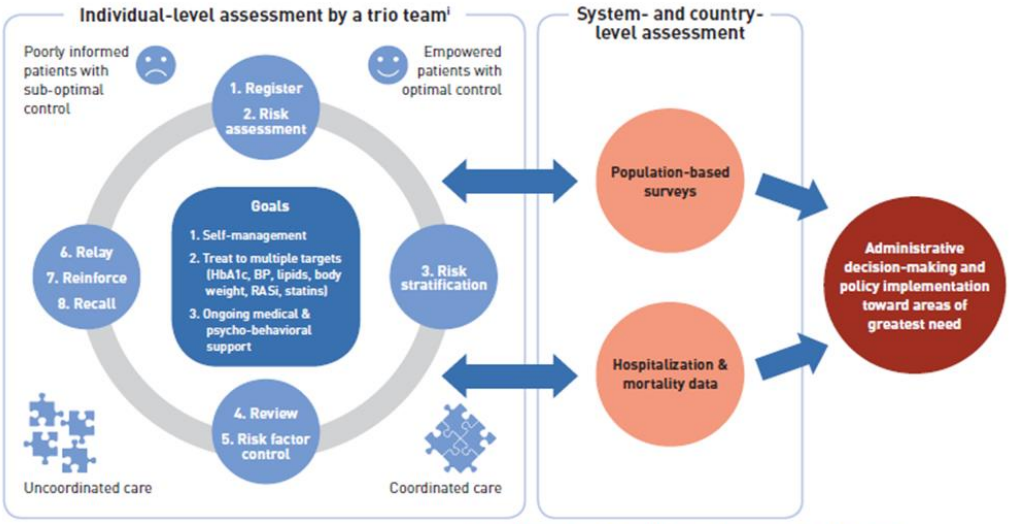
With the growing number of medications, most practice guidelines recommend periodic assessments of risk factors and comorbidities in order to individualise treatment targets and regimens.[247] To achieve these objectives, there is a need to establish a workflow to collect data systematically to stratify risk, triage care and personalise management. These diabetes registers, once established, can serve multiple purposes. On a patient level, the data can be used to provide feedback and individualise care. On a system level, these data can identify care gaps and benchmark performance. On a policy level, these data can be linked to population and hospitalisation data to identify root causes and monitor disease patterns and burden (Figure 12).[439]

Although not universally applicable, there are now institutional or national attempt to establish EMR systems by digitalising patient-related information collected during routine practice. These data management systems are usually well-designed, supported by good practices including privacy protection. Depending on the complexity of the system, the data types include demographics, hospitalisation, insurance claims and medications. These EMR systems can facilitate patient management including the 'pay for performance' schemes in England[440] and Taiwan in the field of diabetes.[441] Other workers have designed simple databases and change workflow to capture essential information during annual comprehensive assessment to set up diabetes registers for quality improvement. From a clinical perspective, once data are systematically collected, especially if relayed back to HCPs, patients and their caregivers, improvement in care standards often follows, in part due to improved awareness and self-management as well as intensified treatment with better adherence.[442]

### *9.5 A step-by-step implementation plan to deliver a data-driven integrated diabetes care plan*

Many countries are now adopting the WHO recommendation to provide universal health coverage including essential medicines (metformin, SU, insulin, statin, RASi, aspirin). However, to ensure the appropriate and effective use of these medicines, the health system needs 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.[443-446] Self-management, promoted by structured diabetes education, is the cornerstone of successful diabetes care.[260] In HICs, professional organisations have stipulated the credentials of educators and curriculum of diabetes self-management and education.[447] In LMICs and resource-constrained settings, trained physicians and nurses will need to take on the trainer and manager roles to transfer knowledge, develop care protocols, design workflows and train HCA to take on these assessment and education tasks, while doctors focus on making clinical decisions, prescribing drugs and looking after patients with more complex problems. In high-income areas, better care organisation with task shifting to facilitate team-based care can also lead to better efficiency and affordability with lower patient default rate and better job satisfaction for the workforce.[448]

**Figure 12. A schematic diagram showing how fragmented care can transform into data-driven, integrated diabetes care using a trio team including trained nurses and healthcare assistants, supervised by physicians, to collect data systematically during routine clinical practice to establish a register and use the data to empower self-management and treat to multiple targets with ongoing support. The data can be linked to population-based surveys and hospitalisation and mortality date for audit and surveillance purpose to influence policies and practices.**




International Diabetes Federation. IDF Diabetes Atlas, 9th Edition http://www.diabetesatlas.org/ accessed 2nd May 2020

Based on care models which are already in operation in some areas and in accordance with international guidelines,[247] members of this Commission have provided a template to help HCPs/planners/financers to initiate a structured and integrated assessment, education and support programme (Panel 2), which can be implemented even in low-resource settings. These integrated services can be supervised by physicians but implemented by non-physician personnel including nurses, HCA, trained college graduates or peers with diabetes, if nurses are in short supply (Figure 12).[448,449] In the last decade, a growing number of studies have demonstrated the effectiveness of structured patient education and support programmes delivered by trained community health workers/peers in underserved communities in HICs and to a lesser extent in LMICs.[450-452] In a systematic review of 118 randomised diabetes self-management education (DSME) programmes (defined as single, discrete DSME intervention with one or more follow-up assessment of $HbA_{1c}$ at 3-month interval or greater), contact time of 10 hours or more was associated with significant $HbA_{1c}$ reduction compared with exposure of less than 10 hours. More than 12 months of DSME intervention was more likely to achieve significant $HbA_{1c}$ reduction than those lasted ≤2.5 months. The benefit was most evident in those with $HbA_{1c}$>9% (75 mmol/mol), where intervention could lead to reduction of $HbA_{1c}$ as much as 0.7% (7.7 mmol/mol), with more than 70% of patients showing significant improvement.[453]

Panel 2 summarises the facilities, equipment and procedures required to deliver an integrated assessment, education and supporting service delivered by a trained nurse-HCA team including the time-scheduling of these sessions and person-hours required for a 'unit' of 800 patients. The panel stipulates how a typical week can be divided into sessions where non-physician personnel can be trained to gather clinical information, collect blood/urine samples and perform eye (e.g., visual acuity, fundus camera) or foot examination (e.g., sensation and pulses) to assess control of risk factors and detect complications. Depending on case complexity, a patient may need up to one hour to undergo a structured assessment at presentation and every 2–3 years thereafter for quality assurance. For newly-diagnosed patients, longer duration of education/contact time is recommended (e.g., 10 hours over 12 months in groups of 10)[453] are recommended. The content should include nature of disease, treatment targets, regular follow-up and monitoring, healthy lifestyles, medication adherence, sick day management and other special issues (e.g., planning for pregnancy, stress management). This can be followed by individualised sessions based on the risk profiles and needs of the patient.[260,454] Given a total of 3,840 person-hours of a nurse-HCA team, we estimated that 1,600 person-hours can be used to perform structured assessment and 1,200 person-hours for group education with the remaining 1,040 hours used

to provide additional support as needed (Panel 2). Once these patients are stabilised and educated, less time will be required and the team can then take on other tasks such as detecting individuals with undiagnosed or at risk of having diabetes, e.g., positive family history, obesity, history of gestational diabetes, polycystic ovary syndrome, hypertension, dyslipidaemia, NAFLD, smoking or high risk scores for early intervention.[365]

To maximise efficiency, clerical staff and/or HCA can be trained to perform simple measurements (e.g., BP, body weight, body height, waist circumference), collect biosamples (urine and blood), ask non-clinical questions (e.g., demographic data, 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 EMR. Alternatively, these databases can stand alone and periodically linked to other administrative databases for monitoring of outcomes. Even in areas without EMR, personal computers can be used to digitalise these paper-and-pen registers to enable patient recall every 2–3 years to avoid default and ascertain clinical outcomes including death.

Importantly, these 'structured' protocols for data-gathering together with continuing care by the same diabetes team with ongoing evaluation can facilitate on-the-job training and motivate members to champion these evidence-based care models.[323,455] Once 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 (e.g., young patients, elderly patients, patients with obesity, patients with multiple medications including insulin injections, patients with psychosocial stress or poor adherence).[456] In some settings, notably in LMICs pending healthcare investments and reforms, co-sharing of facilities and staff time for management of complex diseases (e.g., tuberculosis, HIV infection) can kick-start and expedite the formation of these diabetes teams to provide data-driven, integrated care for these diseases requiring long-term care.[167,457,458]

Due to the continuing nature of diabetes management encompassing prevention, diagnosis, treatment and rehabilitation and depending on the healthcare financing and workforce development in each country/area, these community-based diabetes teams with linkage to specialist-led Diabetes Centre should preferably have a predefined provider:patient ratio to avoid over- or under-utilisation of these resources. Based on existing models, we estimate that 0.25–0.50 physician supported by one nurse, one HCA and one clerical staff will be able to manage 800–1,600 patients on a recurring basis (depending on their risk profiles) as well as implement primary prevention programmes. The efficiency of this data-driven, integrated programme can be further enhanced using ICT, mobile health and peer support.

### *9.6 An example of using research-driven quality improvement initiatives to transform care and inform policies*

In Hong Kong, a research-driven quality improvement programme run by trained non-physician personnel, initiated at a university-affiliated hospital to overcome manpower shortage in early 1990s, evolved to become a territory-wide risk assessment and management programme.[459] Using 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. Based on 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 decision support to promote shared decision-making between patients and HCPs. Similar to the UKPDS Outcome Model,[460] data from the Hong Kong Diabetes Register were linked to hospitalisation records using unique identifier which 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 with display of trends of risk factor control and future risk of complications using bars and trend lines. These personalised data were accompanied by recommended treatment targets and decision support triggered by attained targets. By using technologically-assisted, data-driven integrated care, we can empower self-management, reduce clinical inertia, personalise care and monitor care quality. Through these regular assessments, the care

team can also identify patients with unstable control and complex phenotypes such as those with YOD, atypical presentations, emotional distress and frailty.[439,461] Thus, despite the large volume of patients and complex care protocols, it is possible to start improving the quality of care by using teams, logistics and data analytics to improve the efficiency and quality of care. By demonstrating better 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.[462,463]

In 2000, the hospital administrators created career paths for diabetes nurses to scale up the operation of these Diabetes Centres dedicated to providing assessment (eye, feet, blood/urine), education and care coordination. To date, in this city of 7.5 million population, 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, community-based primary care clinics offer similar risk assessment and management programme (RAMP-DM), enhanced by incorporation of the protocol of the JADE Programme.[464] In a 5-year evaluation analysis involving patients with 8 years of disease duration and without micro/macrovascular complications, the relative risk of any clinical event including death was reduced by 50% in the RAMP-DM participants, many of whom were also referred to a patient empowerment programme, compared with a propensity score-matched cohort.[465] In a subsequent cost-effectiveness analysis, the ARR of the RAMP-DM ranged from 3 to 13% and the NNT ranged from 7 to 68. Using existing infrastructures in the primary care setting and taking into account the implementation cost of USD 157 per individual including set up and ongoing cost, e.g., purchase of fundus camera, incorporating risk algorithms into the EMR and training nurses to perform the procedures and patient education, there was an average reduction of USD 7,000 over 5 years after considering all the costs incurred during hospital visits (consultations, drugs, investigations and procedures).[465] This cost-saving was due to the 2–9 times higher costs of these complications compared with the base costs.[466] Taken together, this territory-wide quality improvement initiative supports the clinical benefits and cost-saving nature of using information technology, logistics and data-driven integrated care, focusing on patient empowerment, feedback and treatment of multiple targets.[463]

Panel 3 shows a list of clinical and laboratory data which can be collected periodically and the JADE risk stratification and care model which has been adapted by the aforementioned territory-wide RAMP-DM with proven benefits and cost-effectiveness.[464,467] By documenting these risk profiles at presentation and every 18–24 months thereafter, we 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. These diabetes registers when linked to EMR/hospitalisation data or other disease registers (e.g., ESKD, myocardial infarction, cancer, death) using a unique identifier 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 within- and between-country differences in causes, trajectories and consequences of diabetes. By using attainment of treatment targets, access to structured education programmes and prescription of organ-protective drugs as performance indexes for benchmarking purposes, we can also promote best practices. These real-world effectiveness data complement efficacy data from RCTs in controlled settings[278,468] to guide clinical practice, as well as identify subgroups most likely to benefit or develop adverse events.[439,469]

### *9.7 Use Specialised Diabetes Centres to promote research and professional education*

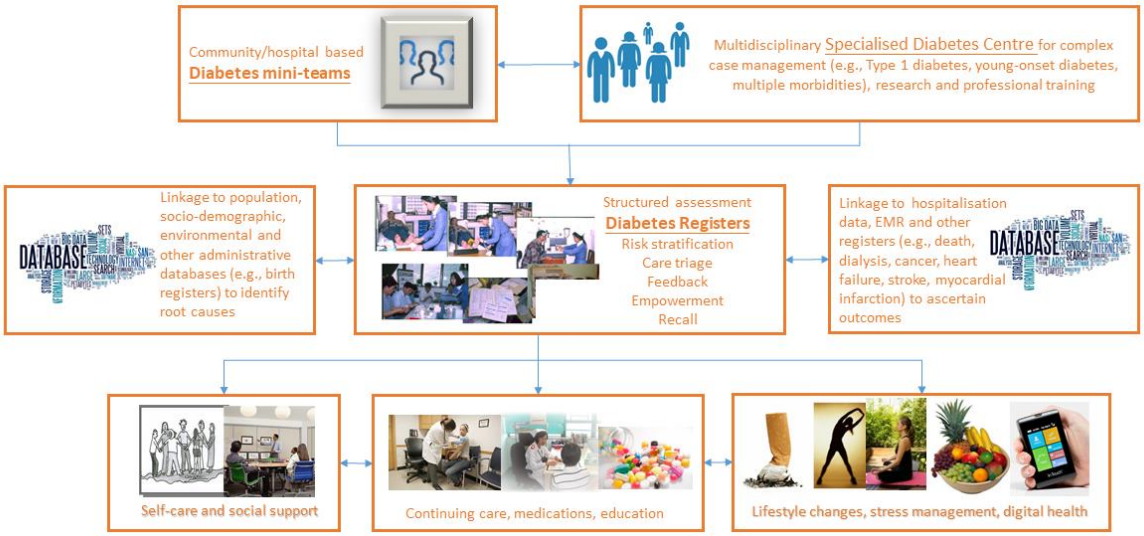
Professional education is a prerequisite to good clinical care and effective patient education. Using insulin treatment as an example, large-scale audits often revealed inappropriate use of insulin (timing, regimen, dosages) by untrained HCPs with adverse consequences. In real-world practice, there are considerable delays in the initiation and intensification of insulin, with a lag period of 4–8 years in patients with T2D, resulting in prolonged exposure to hyperglycaemia.[470] Even if insulin is initiated, lack of titration and self-discontinuation are not uncommon. Inappropriate insulin regimens and excessive use of blood glucose lowering drugs can cause severe hypoglycaemia, which is a leading cause of emergency hospitalisation especially in the elderly.[241] Patients with multiple morbidities and polypharmacy will need periodic review of their medications to ensure safety.[471] In the cluster-randomised 'Stepping up' Program conducted in Australia, an accredited diabetes nurse educator served

as mentor and trained nurses working in primary care clinics to initiate and titrate insulin in patients with T2D who needed insulin therapy. Compared with the 'control clinics', 70% of patients managed by these trained nurses in the 'intervention clinics' were started on insulin compared with 22% in the 'control clinics' with a 0.6% (6.6 mmol/mol) difference in $HbA_{1c}$ in favour of the 'intervention clinics'.[472]

Diabetes management has now become increasingly complex with many technological advancements, such as the use of multiple medications and injectables, continuous glucose monitoring, insulin delivery systems and metabolic surgery. There are also emerging technologies such as using biogenetic markers in precision medicine.[473] To ensure that patients get the full benefits of these advancements, there is a need to expand the curriculum of undergraduate programmes with ongoing postgraduate and professional training in diabetes and other NCDs. Attending regular conferences organised by professional organisations is essential for updating professional knowledge in order to improve care. Besides, hospital- or community-based specialised Diabetes Centres, often affiliated with academic institutions or major healthcare organisations are in a good position to set up accreditation programmes in diabetes management and education (e.g., Certificate, Diploma or Master courses). These programmes will help build a critical 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[247] including the IDF.[389,474]

These Centres, whether based in LMICs or HICs, should have a dedicated space led by one or more physicians with credentials in diabetes management and nurses with training in diabetes education supported by appropriate equipment and tools (Panel 2). These Centres are usually tasked with management of patients with complex needs, such as T1D, YOD, MODY, T2D with comorbidities including depression, supported by other healthcare professionals (e.g., dietitians and podiatrists) and specialists (e.g., ophthalmologists, metabolic surgeons, cardiologists, nephrologists, psychiatrists) and work closely with primary care physicians to provide collaborative care. For quality improvement and research purposes, these Centres are recommended to establish registers and ensure patients are seen at the right time by the right team in the right setting to achieve the best outcome.[415] By combining practice, research and professional training, these Centres can take on additional roles of monitoring performance, analysing registers and developing new programmes to address unmet needs (Figure 13). In a prospective cohort of 7,488 patients with T2D (1986–1991) followed up in Italy, patients seen only by family physicians had a higher mortality than the general population with a SMR of 1.62 (95% CI 1.51–1.74). This fell to 1.44 (1.34–1.54) among patients attending both family physicians and Diabetes Centres. The respective 5-year survival probabilities were 0.76 (0.75–0.78) and 0.81 (0.80–0.82) compared with the general population. Attending the Diabetes Centres was an independent predictor of improved survival, after adjusting for sex, age and diabetes therapies. Similar benefits were observed for cardiovascular death.[475,476]

**Figure 13. A schematic diagram showing the combined use of Specialised Diabetes Centres, diabetes teams and diabetes 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.**



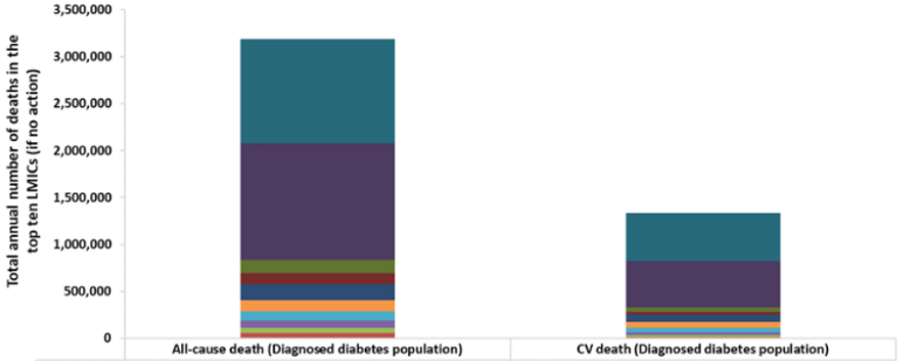

## 10 Use simulation models to estimate and compare the impacts of 'no action' versus 'action'

In this evidence-based document, we put great emphasis on the inter-dependency of society, community and individuals in influencing outcomes. In the case of T1D, we have quantified the impacts of provision of comprehensive care in reducing premature death in young individuals (Section 6.4). For T2D, rapid societal changes have changed our ecosystem, way of living and access to care especially in LMICs, which explain a large fraction of the epidemic, albeit potentially preventable. The health consequences of this epidemic will in turn have societal consequences, notably healthcare expenditure, societal productivity and quality of life. The complex pathophysiology of diabetes has led to many faces of diabetes while individuals with diabetes and those at risk have many needs, beyond medical. Over the last three decades, we have gathered a wealth of data regarding the size of the problem and effects of potential solutions. In the current section, we have used these data to develop two models to quantify the burden of diabetes and the impacts of an integrated prevention and care programme in T2D. The methodologies of these models are detailed in the Supplemental Materials. These models are available on line to allow readers to enter local data and estimate potential effects of implementing various strategies in their countries/areas, organisations and/or clinic practices.

### *10.1 Use IDF, WHO and RCT data to estimate the effects of care access on reducing death and CVD in T2D*

To quantify the impact of this integrated society-community-individual strategy (Figure 10), we compared the effects of 'no action' versus 'action' by reducing multiple risk factors. We first used the 2016 WHO Global Health Estimates on causes of death[11] and 2017 IDF World Diabetes Atlas on diabetes prevalence in the 30–69 age group.[3] We then used the hazard ratios of all-cause (1.8) and CVD-related deaths (2.3) associated with diabetes (including diagnosed and undiagnosed) versus those without diabetes as reported in the Emerging Risk Factor Collaborative Cohort,[1] to estimate the total number of deaths attributable to diabetes (refer to Supplemental Material for details of methodology). Based on these assumptions, we selected the top 10 LMICs with the largest population with diabetes, which account for 50% of the global diabetes population. We modelled that amongst these 109 million individuals (aged 30–69 years) diagnosed with diabetes living in these 10 LMICs, an estimated 3.2 million individuals die after 3 years, of whom 1.3 million would be due to CVD (Figure 14).

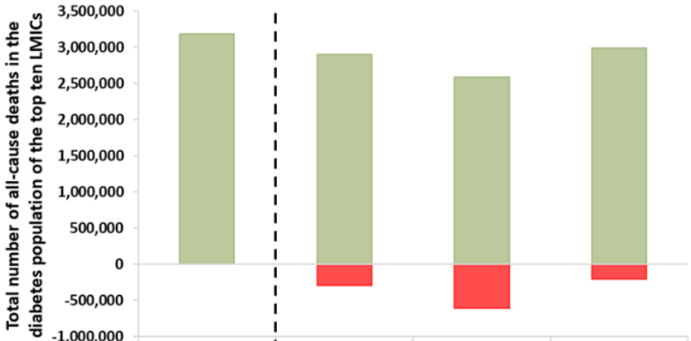
**Figure 14. 3-year estimation of all-cause and CV-death in people with diagnosed diabetes (aged 30-69 years) in the top ten LMICs using WHO and IDF data (2017) and estimated HR of 1.8 (all-cause death) and 2.32 (CV-death) for diabetes based on the Emerging Risk Factors Collaboration.**




| | All-cause death (Diagnosed diabetes population) | CV death (Diagnosed diabetes population) |
|---|---|---|
| China | 1,111,194 | 507,880 |
| India | 1,239,506 | 497,537 |
| Brazil | 140,759 | 46,353 |
| Mexico | 118,833 | 26,055 |
| Indonesia | 173,452 | 80,204 |
| Egypt | 118,609 | 60,875 |
| Pakistan | 99,834 | 49,808 |
| Bangladesh | 74,289 | 31,653 |
| Turkey | 56,205 | 18,585 |
| Thailand | 56,355 | 13,252 |
| Total | 3,189,035 | 1,332,200 |

The use of statins which are available at extremely low costs for generic preparations (even in LMICs) to reduce LDL-cholesterol by 1 mmol/L (39 mg/dL) can lower the risk of all-cause death by 9%[477] and CVD and related death by 13%,[211] especially in patients with diabetes with either high cardiovascular risk or LDL-cholesterol ≥2.6 mmol/L (100 mg/dL). While reducing $HbA_{1c}$ by 1% (11 mmol/mol) may lower CVD events[208] or cardiovascular death by 10%[209] and reducing systolic BP by 10 mmHg by 20%[210], we estimate that each of these interventions can reduce CVD and/or all-cause death by 10–20% (Table S1). Although the levels of $HbA_{1c}$, BP and LDL-cholesterol are not known in these populations, we assume that the majority of diagnosed individuals with diabetes can benefit from further reduction in risk factors. Assuming a diagnosis rate of 50% and by ensuring access to essential medicines including statins, blood glucose and BP-lowering drugs in at least 70% of these diagnosed individuals, together with a supporting system to ensure sustained reduction of these risk factors for three years, we can potentially avert between 300,000 and 600,000 premature deaths by reducing BP by 10 mmHg, depending on their baseline BP. By treating them with statins to reduce LDL-cholesterol by 1 mmol/L (39 mg/dL), we can avert another 200,000 all-cause deaths, thereby averting up to 800,000 premature deaths (Figure 15A). By improving each of these three risk factors ($HbA_{1c}$, LDL-cholesterol and BP), we can potentially avert between 30,000 and 240,000 cardiovascular deaths depending on their baseline risk factors (Figure 15B).

**Fig 15A. 3-year estimation of total number of all-cause deaths with status quo and all-cause deaths averted with interventions in the diagnosed diabetes population aged 30-69 years from the top 10 LMICs**




| | No-Action | SBP -10mmHg | SBP -10 mmHg (SBP≥140) | LDLC -1 mmol/L |
|---|---|---|---|---|
| Deaths_Total | 3,189,035 | 2,898,833 | 2,586,307 | 2,988,126 |
| Deaths_Averted | | -290,202 | -602,728 | -200,909 |
| DM population | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) No change in diabetes prevalence and death rate for 3 years; 4) Death rate = birth rate; 5) Sustained effect size for 3 years*

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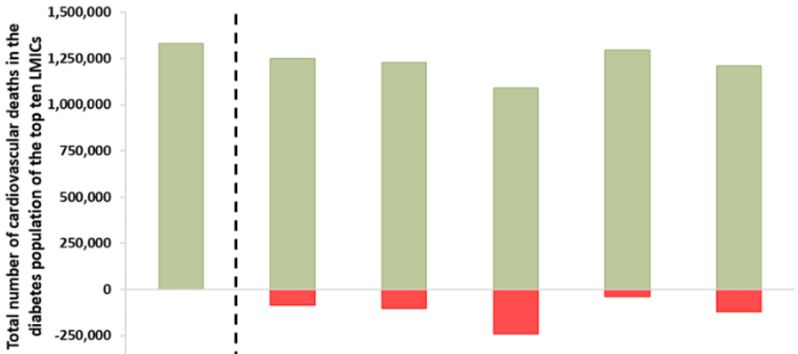
**Fig 15B. 3-year estimation of total number of CV deaths with status quo and CV deaths averted with interventions in diagnosed diabetes population aged 30-69 years from the top 10 LMICs**




| | No-Action | A1C -0.9% | SBP -10mmHg | SBP -10 mmHg (SBP≥140) | SBP -10 mmHg (SBP<140) | LDLC -1 mmol/L |
|---|---|---|---|---|---|---|
| Deaths_Total | 1,332,200 | 1,248,272 | 1,229,621 | 1,089,740 | 1,294,899 | 1,210,970 |
| Deaths_Averted | | -83,929 | -102,579 | -242,460 | -37,302 | -121,230 |
| DM population | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) No change in diabetes prevalence and death rate for 3 years; 4) Death rate = birth rate; 5) Sustained effect size for 3 years*

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### *10.2 Use observational data to develop a risk calculator and use RCT data to estimate effects of intervention*

Each person with diabetes is unique with different risk factors, trajectories, complications and outcomes which can be modified by improving access to care, education and medications, as well as changing behaviours and social habits.[478] In our literature search, there are very few country/territory-wide registers with comprehensive data including non-modifiable (e.g., age, sex, duration of diabetes, complications) and modifiable risk factors (e.g., $HbA_{1c}$, BP, LDL-cholesterol, BMI, use of tobacco, self-management, lifestyles) linked to clinical outcomes. Some of these registers come from small countries or areas such as Sweden and Hong Kong, in part due to their small population size. In these countries/areas, the linkage of clinical records to national disease registers or EMR/hospitalisation records can be facilitated by unique identifiers and the use of International Classification of Diseases (ICD) codes.[59,479] Similar to the UKPDS Outcome Model including risk equations based on data collected in a RCT setting,[460,480] risk equations can be developed using these real-world databases, although its external validation may be confounded by ethnicity, locally-relevant risk factors and care standards.[481,482] That said, these models with absolute risk prediction, can provide useful information

regarding the effects of reducing different risk factors using different strategies which can help HCPs or planners prioritise their action plans.

### *10.3 Use $HbA_{1c}$, BP, LDL-cholesterol to develop an 'ABC' model and estimate effects of integrated care in 3 years*

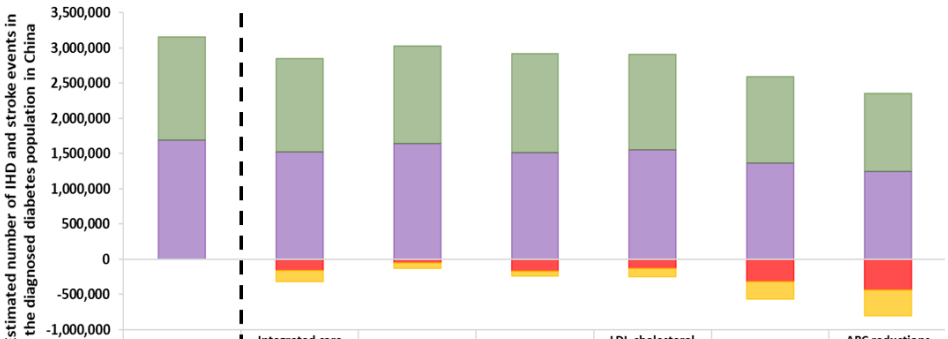
Although we have curated 40 cross-sectional surveys to provide a global landscape of risk factor distribution in 1.9 million people with T1D or T2D, most of these surveys reported only basic information and did not have details on cardiovascular complications and renal function which are important prognostic factors (Figure 6). We therefore used commonly reported variables (age, sex, duration of diabetes, use of tobacco, $HbA_{1c}$, systolic/diastolic BP, LDL-cholesterol and BMI) available in the Hong Kong Diabetes Register and the JADE Register consisting of 22,514 patients with T2D (1994–2015) observed for 65,966 patient-years since 1994,[483]and used Poisson regression analysis[484] to develop an 'ABC' model to estimate the incidence of CVD (including ischaemic heart disease and stroke) and related death up to 3 years.

We externally validated this model by using the published summary data of two prospective cohorts with reported events. These included the Hong Kong Diabetes Database consisting of 212,659 Chinese patients with T2D and the National Swedish Diabetes Register consisting of 96,673 with imputed data for 271,174 non-Chinese patients with T2D (Table S2). By simulating one million patients with similar profile, the ABC model performed well with risk ratio of predicted versus observed events approaching 1 (Table S3). Using this validated model, we can estimate the 3-year incidence rate of CVD in diabetes populations (aged 20-79 years) with different combinations of risk factors. We then estimated the impact of reducing each or all three ABC risk factors using the RRR reported in RCTs[208-211] (Table S1) based on medications alone with or without provision of integrated care,[275] the latter aimed at overcoming clinical inertia and non-adherence.[268]

We selected two published cohorts with data needed to run the ABC model. In the China NCD Surveillance Cohort which included predominantly newly-diagnosed individuals,[485] the mean $HbA_{1c}$ was 7.2% (55 mmol/mol), systolic BP, 144 mmHg and LDL-cholesterol, 2.59 mmol/L (100 mg/dL). In China, 10% of adults have diabetes.[381] Assuming a 50% diagnosis rate (57 million) with risk profiles similar to the China NCD Surveillance Cohort,[485] with 70% of these diagnosed patients under usual care, we estimated that 3 million of them may develop a CVD 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 BP by 2.4 mmHg, and LDL-cholesterol by 0.14 mmol/L (5.4 mg/dL)[275] to at least 70% of these diagnosed individuals, we could avert 300,000 CVD events.

If we intensify control of risk factors using medications to lower $HbA_{1c}$ by 0.5% (5.5 mmol/mol), LDL-cholesterol by 0.5 mmol/L (19 mg/dL) and systolic BP by 5 mmHg, we could avert between 130,000 and 250,000 CVD events. If all three risk factors are improved, we can avert 570,000 CVD events which increases to 800,000 events if this is combined with integrated care (Figure 16A). We used the published costs of diabetic complications in a public healthcare setting in Hong Kong[466] adjusted for cost of living index, we estimated the potential cost saving in these scenarios (refer to Supplemental Material). If status quo is maintained, these CVD events will cost the system over USD 5,200 million which can be reduced by USD 1,300 million if care is organised along with increased use of medications to reduce multiple risk factors (Figure 16B).

**Fig 16A. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (community-based): Estimated incidence of ischaemic heart disease (IHD )and stroke, and events averted with interventions**




| | No-Action | Integrated care (IC) | HbA1c -0.5% | SBP -5 mmHg | LDL-cholesterol -0.5 mmol/L | ABC reductions | ABC reductions combined with IC |
|---|---|---|---|---|---|---|---|
| IHD_Incidence | 1,470,865 | 1,321,440 | 1,382,673 | 1,407,115 | 1,350,582 | 1,221,214 | 1,108,020 |
| STK_Incidence | 1,686,567 | 1,522,873 | 1,640,356 | 1,514,673 | 1,555,308 | 1,367,432 | 1,247,987 |
| IHD_Averted | | -149,425 | -88,191 | -63,750 | -120,283 | -249,651 | -362,845 |
| STK_Averted | | -163,695 | -46,211 | -171,894 | -131,259 | -319,135 | -438,581 |
| Total_Incidence | 3,157,432 | 2,844,312 | 3,023,030 | 2,921,787 | 2,905,890 | 2,588,645 | 2,356,007 |
| Total_Averted | | -313,120 | -134,402 | -235,644 | -251,542 | -568,786 | -801,425 |
| DM Population | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. ABC refers to Hb**A**$_{1c}$, systolic **B**lood pressure and LDL-**C**holesterol.*

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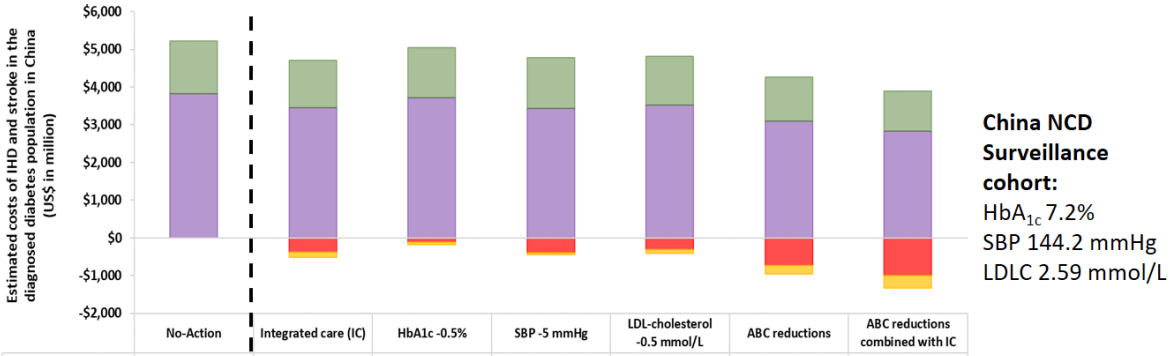
**Fig 16B. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (community-based): Estimated costs incurred and saved for ischaemic heart disease (IHD) and stroke with interventions**




| | No-Action | Integrated care (IC) | HbA1c -0.5% | SBP -5 mmHg | LDL-cholesterol -0.5 mmol/L | ABC reductions | ABC reductions combined with IC |
|---|---|---|---|---|---|---|---|
| IHD_cost incurred | $1,399 | $1,257 | $1,315 | $1,338 | $1,285 | $1,162 | $1,054 |
| Stroke_cost incurred | $3,829 | $3,457 | $3,724 | $3,438 | $3,531 | $3,104 | $2,833 |
| IHD_cost saved | | -$142 | -$84 | -$61 | -$114 | -$237 | -$345 |
| Stroke_cost saved | | -$372 | -$105 | -$390 | -$298 | -$724 | -$996 |
| Total_cost incurred | $5,228 | $4,714 | $5,039 | $4,777 | $4,815 | $4,266 | $3,887 |
| Total_cost saved | | -$514 | -$189 | -$451 | -$412 | -$962 | -$1,341 |

a. *The combined public and private direct medical costs per event in China: US$ 951 for CHD, US$ 2,270 for stroke (assumed no baseline complications).*
b. *CKD, ESRD and PVD are excluded in the calculation and thus, these are underestimations. *Integrated care (task shifting).*
c. *Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. ABC refers to Hb**A**$_{1c}$, systolic **B**lood pressure and LDL-**C**holesterol.*

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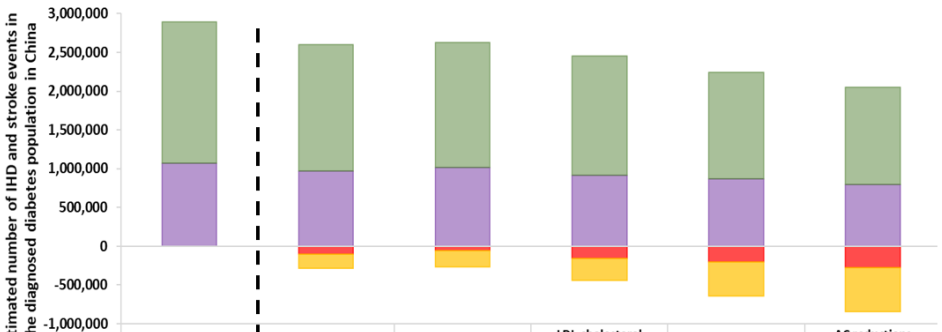
In a clinic-based cohort of Chinese patients with T2D enrolled in the JADE Register,[486] the mean disease duration was 5 years. Compared with the China NCD Surveillance Cohort,[485] these patients had better BP control but higher $HbA_{1c}$ and LDL-cholesterol levels ($HbA_{1c}$ 7.9% [63 mmol/mol], BP 125.8 mmHg, LDL-cholesterol 2.94 mmol/L [114 mg/dL]). Assuming a 50% diagnosis rate with similar risk profiles, if we can reduce $HbA_{1c}$ 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 CVD events and USD 1,400 million will be saved (Figure 17A/B).

**Fig 17A. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (clinic-based): Estimated incidence of ischaemic heart disease (IHD) and stroke, and events averted with interventions**



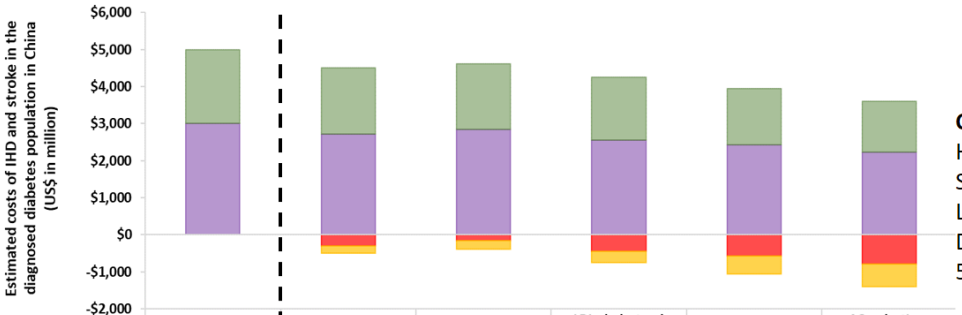

**China JADE study:**
$HbA_{1c}$ 7.9%
SBP 125.8 mmHg
LDLC 2.94 mmol/L
Disease duration
5 years

| | No-Action | Integrated care (IC) | HbA1c -1% | LDL-cholesterol -1 mmol/L | AC reductions | AC reductions combined with IC |
|---|---|---|---|---|---|---|
| IHD_Incidence | 1,818,568 | 1,634,014 | 1,610,119 | 1,538,509 | 1,375,918 | 1,255,538 |
| Stroke_Incidence | 1,075,112 | 970,671 | 1,017,148 | 917,071 | 871,279 | 795,126 |
| IHD_Averted | | -184,554 | -208,450 | -280,060 | -442,650 | -563,031 |
| Stroke_Averted | | -104,441 | -57,964 | -158,042 | -203,833 | -279,987 |
| Total_Incidence | 2,893,681 | 2,604,686 | 2,627,267 | 2,455,580 | 2,247,197 | 2,050,663 |
| Total_Averted | | -288,995 | -266,414 | -438,101 | -646,484 | -843,018 |
| DM Population | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. AC refers to Hb**A**$_{1C}$ and LDL-**C**holesterol.*



**Figure 17B. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (clinic-based): Estimated costs incurred and saved for ischaemic heart disease (IHD) and stroke with interventions**




**China JADE study:**
$HbA_{1c}$ 7.9%
SBP 125.8 mmHg
LDL-C 2.94 mmol/L
Disease duration
5 years

| | No-Action | Integrated care (IC) | HbA1c -1% | LDL-cholesterol -1 mmol/L | AC reductions | AC reductions combined with IC |
|---|---|---|---|---|---|---|
| IHD_cost incurred | $1,999 | $1,796 | $1,770 | $1,691 | $1,512 | $1,380 |
| Stroke_cost incurred | $3,004 | $2,712 | $2,842 | $2,563 | $2,435 | $2,222 |
| IHD_cost saved | | -$203 | -$229 | -$308 | -$487 | -$619 |
| Stroke_cost saved | | -$292 | -$162 | -$442 | -$570 | -$782 |
| Total_cost incurred | $5,003 | $4,509 | $4,612 | $4,254 | $3,947 | $3,602 |
| Total_cost saved | | -$495 | -$391 | -$749 | -$1,056 | -$1,401 |

a. *The combined public and private direct medical costs per event in China: US$ 1,099 for CHD, US$ 2,794 for stroke (assumed no baseline complications).*
b. *CKD, ESRD and PVD are excluded in the calculation and thus, these are underestimations. *Integrated care (task shifting).*
c. *Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. AC refers to Hb**A**$_{1C}$ and LDL-**C**holesterol.*



We acknowledge the considerable inter-country variations in healthcare financing (public, private, partially subsidised) and provider systems (single care provider versus multiple care providers). However, based on published epidemiological and RCT data, this case study illustrates the potential impacts of improving access to medications, continuing care and patient education at a system level, which can prevent millions of CVD events and save billions of dollars. In this case study, 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 Chinese with different risk profiles in both public and public-private partnership settings.[57,459] 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 amongst the affected workforce.

### *10.4 Use a simulation model to estimate the impact of a 20-year society-community-individual T2D prevention strategy*

We developed a simple Markov microsimulation model[204] to evaluate the short-, mid- and long-term impact of an integrated strategy for preventing T2D and CVD, compared with a status quo or non-intervention. This multicomponent strategy include education-social-environmental policies, population-based health promotion policies as well as early detection, prevention and treatment programs. The model was developed for meeting the particular need of this Report, i.e., the model needs to be:

1. flexible for applying the model in a diverse country setting
2. less data-demanding and make use of data available in most countries especially low-income countries and
3. able to capture the main health impact of the preventive programmes (refer to Supplemental Material).

Using published data from China,[487] Hong Kong[488] and Brazil,[364] we estimate the distribution of risk categories for progression to T2D and the number of T2D and CVD events averted if a hypothetical multicomponent intervention is implemented in one million individuals in 5, 10 and 20 years compared to 'status quo'. The total effect size of this society-community-individual strategy[489] is inferred from the relative risks associated with modifiable risk factors reported in observational studies (Table 2) and RCTs using lifestyle interventions and medications (Table 4).

Assuming the best scenario where governments, regulators, funders, practitioners, industry and community act in concert to transform the ecosystem and establish community-based facilities to raise awareness and identify high-risk individuals for early intervention with linkage to an integrated healthcare system, we can create maximal impacts at all levels to reduce T2D and CVD events in a 20-year horizon. We assume that a societal strategy will reduce the risk of progression from low risk to high risk for diabetes by 5% while a combined population- and individual-based approach will reduce the risk of progression to T2D and CVD both by 25%. Based on reports from population-based surveys,[364] we assume the annual incidence of diabetes in the high risk group (e.g. prediabetes, metabolic syndrome) to be 1.9%, 3.8% and 3.8% in the <45, 45-60 and >60 age groups, respectively. The corresponding figures for annual progression from low to high risk for diabetes are 5, 8 and 10%. The annual incidence of CVD is estimated from the 2013 American College of Cardiology/American Heart Association Atherosclerosis Cardiovascular Disease (ACC/AHA ASCVD) risk equation using common risk factors including age, sex, smoking, lipids, $HbA_{1c}$ and BMI.[490]

1) Societal strategy
    a) Universal secondary school education
    b) Social inclusion and protection
    c) Environmental protection

2) Population-based health-promoting strategy
    a) Health awareness programme (e.g., public education, social media)
    b) Tobacco control (e.g., price, smoke-free area, media, warnings, tax, cessation support)
    c) Food policies (e.g., price, adverts, labelling, tax, media)
        i) ensure food security
        ii) avoid foods with high sugar, salt, trans fat content
        iii) provide subsidy for healthy foods

3) Community-based detection and prevention programme
    a) Universal health coverage
    b) Strong primary care system
    c) Use risk conditions and risk scores to identify high-risk individuals for primary prevention
    d) Use non-physician personnel to implement diabetes prevention programmes
    e) Use technology to increase reach, effectiveness, adoption and maintenance of diabetes prevention programmes

f) Early use of metformin, RASi and statins in high-risk individuals to prevent T2D and/or CVD

The model estimates the total and cumulative effects of these health policies and system change over a 20-year horizon. The impact of the high-risk population-based strategy such as intensive lifestyle intervention or metformin use applies to the high-risk population for T2D. Early use of organ-protective drugs such as statins and RASi applies to the high-risk population for CVD (e.g., hypertension, obesity, dyslipidaemia). The impact of whole population strategies such as tobacco control, sugar-sweetened beverage tax applies to all groups for reduction of risk factors. The strengthening of healthcare system through capacity building enables early detection and intervention of these high-risk individuals once diagnosed. In support of this multicomponent strategy, there is now evidence suggesting that prevention of T2D will translate into long-term reduction of CVD.[256] While reducing multiple risk factors using statins and RASi can prevent the risk of CVD by 20–40% in high-risk individuals with or without T2D,[372] the implementation of integrated diabetes care can reduce CVD events by 50%.[459]

Figure 18A/B show the distribution of risk factors in a Chinese population stratified by age groups, as well as the estimated rates of progression to prediabetes and T2D in different age groups based on prior knowledge.[487,488] Assuming that we can successfully implement all components within this strategy in an integrated manner, in the next 10 years, for every one million adults, we can avert 22,489 diabetes events and 17,270 CVD events which will increase to 33,733 and 51,863, respectively after 20 years. These figures translate to prevention of T2D in 44 million adults and that of CVD events in 67 million adults for a 1.3 billion population in China alone. Using the same arguments, Figure 19A/19B show similar impacts in Brazil in a population of 130 million in 2017.

**Figure 18A. Risk factor distribution in 1 million Chinese population and using risk equations to project diabetes/CVD events with or without an integrated society-community-individual strategy aimed at improving health environment, reducing population risk and implementing structured lifestyle modification in high risk individuals**

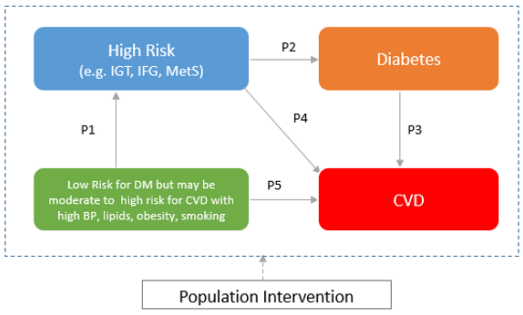


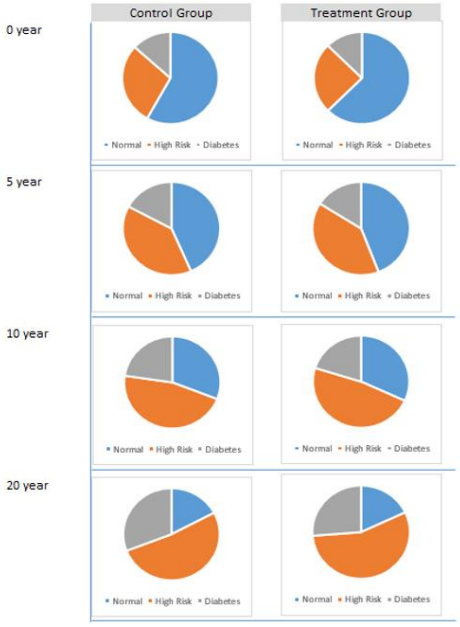

Table 1. Required information for population distribution

| Input Parameters | Age Groups | | |
|---|---|---|---|
| Baseline Demographics | <45 | 45~65 | >65 |
| Number of person to intervene | 300,000 | 300,000 | 400000 |
| Proportion of High Risk persons in the intervention population | 10% | 20% | 40% |
| Proportion of Diabetes in the intervention population | 5% | 10% | 20% |
| Proportion of Smokers in the intervention population | 30% | 30% | 30% |
| Annual probability of developing diabetes amongst those at high risk for diabetes | 1.3% | 3.8% | 3.8% |
| Annual probability of moving to high risk amongst those at low risk for diabetes | 5% | 8% | 10% |

Table 2. Specify the baseline values for diabetes and CVD for the intervention population

| Normal Risk | <45 | 45~65 | >65 |
|---|---|---|---|
| Average HbA1c | 5.5% | 5.5% | 5.5% |
| Average BMI | 21.6 | 23.3 | 23.1 |
| Average SBP | 110 | 119 | 118 |
| Average Total Cholesterol | 4.23 | 4.56 | 4.53 |
| Average HDL-C | 1.30 | 1.30 | 1.30 |
| High Risk | | | |
| Average HbA1c | 6.0% | 6.0% | 6.0% |
| Average BMI | 23 | 25 | 25 |
| Average SBP | 119 | 129 | 128 |
| Average Total Cholesterol | 4.63 | 4.39 | 4.35 |
| Average HDL -C | 1.30 | 1.30 | 1.30 |
| Diabetes | | | |
| Average HbA1c | 8.5% | 8.0% | 7.5% |
| Average BMI | 23 | 25 | 25 |
| Average SBP | 124 | 134 | 133 |
| Average Total Cholesterol | 4.68 | 5.05 | 5.01 |
| Average HDL-C | 1.24 | 1.24 | 1.24 |

**Figure 18B. 20-year projection of diabetes and CVD events in 1 million people in China with or without an integrated society-community-individual strategy.**




| Simulation Results | | |
|---|---|---|
| Number of Diabetes Prevented * | Events | Relative Risk Reduction |
| 5 years | 11065 | 75.33% |
| 10 years | 22489 | 76.24% |
| 20 years | 33773 | 76.43% |
| Number of CVD Prevented * | Events | Relative Risk Reduction |
| 5 years | 6617 | 75.37% |
| 10 years | 17270 | 76.14% |
| 20 years | 51863 | 79.53% |

* (Control-Intervention)

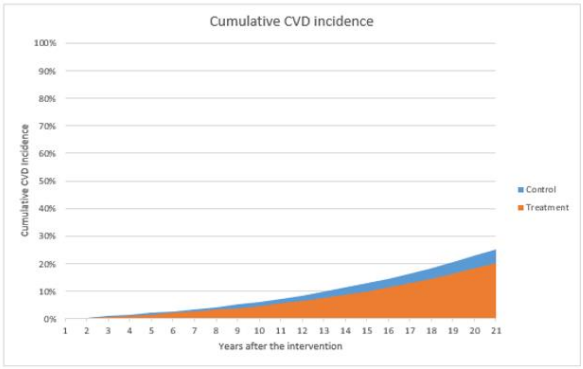



**Figure 19A. Risk factor distribution in 1 million Brazilian population and using risk equations to project diabetes/CVD events with or without an integrated society-community-individual strategy aimed at improving health environment, reducing population risk and implementing structured lifestyle modification program in high risk individuals**

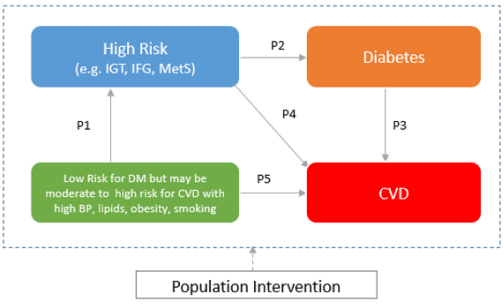


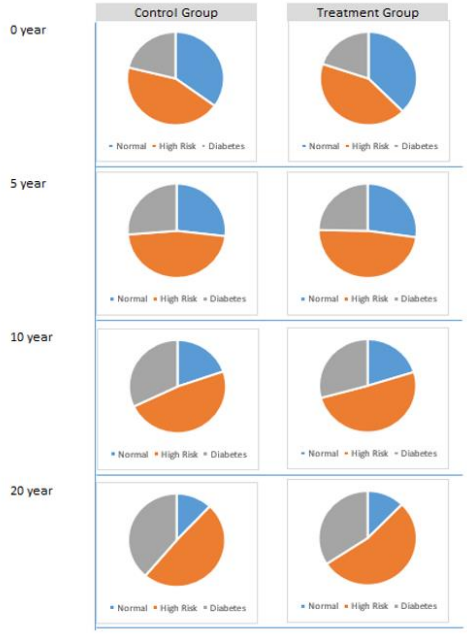

Table 1. Required information for population distribution

| Input Parameters | Age Groups | | |
|---|---|---|---|
| Baseline Demographics | <45 | 45~65 | >65 |
| Number of person to intervene | 300,000 | 300,000 | 400000 |
| Proportion of high risk persons in the intervention population | 34% | 44% | 48% |
| Proportion of diabetes in the intervention population | 6% | 19% | 31% |
| Proportion of smokers in the intervention population | 10% | 14% | 9% |
| Annual probability of developing diabetes amongst those at high risk for diabetes | 1.9% | 3.8% | 3.8% |
| Annual probability of moving to high risk amongst those at low risk for diabetes | 5% | 8% | 10% |

Table 2. Specify the baseline values for diabetes and CVD for the intervention population

| Normal Risk | <45 | 45~65 | >65 |
|---|---|---|---|
| Average HbA1c | 5.07% | 5.18% | 5.31% |
| Average BMI | 25 | 25 | 25 |
| Average SBP | 112 | 117 | 127 |
| Average Total Cholesterol | 5.19 | 5.63 | 5.63 |
| Average HDL-C | 1.5 | 1.6 | 1.7 |
| High Risk | | | |
| Average HbA1c | 5.18% | 5.30% | 5.38% |
| Average BMI | 27 | 28 | 27 |
| Average SBP | 118 | 123 | 131 |
| Average Total Cholesterol | 5.41 | 5.72 | 5.56 |
| Average HDL-C | 1.4 | 1.4 | 1.5 |
| Diabetes | | | |
| Average HbA1c | 6.50% | 6.70% | 6.60% |
| Average BMI | 31 | 29 | 28 |
| Average SBP | 122 | 129 | 135 |
| Average Total Cholesterol | 5.43 | 5.62 | 5.27 |
| Average HDL-C | 1.29 | 1.37 | 1.38 |

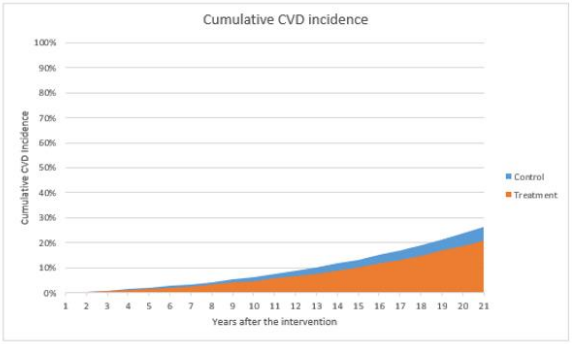
**Figure 19B. 20-year projection of diabetes and CVD events in 1 million people in Brazil with or without an integrated society-community-individual strategy.**




Simulation Results

| Number of Diabetes Prevented * | Events | Relative Risk Reduction |
|---|---|---|
| 5 years | 14407 | 76.01% |
| 10 years | 24564 | 77.38% |
| 20 years | 27997 | 77.83% |
| **Number of CVD Prevented *** | **Events** | **Relative Risk Reduction** |
| 5 years | 6855 | 75.38% |
| 10 years | 17892 | 76.18% |
| 20 years | 52991 | 79.78% |

* (Control-Intervention)




## 11 Use unified data management to track disease burden, measure impacts and inform policies

The total prevalence of diabetes reflects disease burden; age-sex specific prevalence rates allow 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 T2D may reflect impacts of interventions amongst other factors. The latter include but are not limited to, political, socioeconomical and technological changes within a population and/or area. Given the silent and progressive nature of diabetes and its complications, in this section, we discussed the utility of using prospectively designed and unified data management systems to support the collective needs of clinical, surveillance and research activities in order to create impacts.[491]

It is critically important to distinguish the meaning of prevalence, as a measure of disease burden, and 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 this war against diabetes. 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 the prevalence, are other factors that should be considered before prevention programmes are judged as ineffective. Although surveys have been conducted on many millions of individuals across the globe, the data derived from these surveys has serious limitations. For example, of 200 countries analysed by NCD-RisC (NCD Risk Factor Collaboration),[4] 146 had population-based data that included direct measures of glycaemia, but only 108 countries had national data. The countries with the least data were located in central Africa, the Caribbean and Central Asia. Even when studies are available, they sometimes did not enrol younger adults or the elderly. Other limitations of the data include (increasingly) low response rates, especially in HICs, and the use of different definitions of diabetes (e.g., fasting plasma glucose, 75-gram OGTT, $HbA_{1c}$). As a result, it is difficult to compare prevalence between populations and track it over time, even within the same country. For studies using more than one of these measures, the difficulty is compounded by variations in how the measures are combined to define diabetes.

Until recently, the most common source of incidence data has been 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 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 an 'open cohort' design, in which new participants regularly enter the cohort. In practice, this rarely occurs, meaning that alternative sources are needed to determine secular trends.

### *11.1 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. In the earlier section, we have discussed about the use of EMR within the context of using data to identify gaps and improve care. In this section, we presented some of the opportunities in using data analytics for surveillance purposes. With increasing use of digital information, administrative databases are often populated with data from a number of sources, including dedicated disease registers, insurance claims and EMRs. Their strengths include their large size (typically more than 100,000 individual cases), the lack of susceptibility to volunteer bias or loss to follow-up, the capacity to produce year-on-year data at a relatively low cost, and the 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 research settings.

Indeed, unless the data are collected in a structured manner, there is uncertainty about how, and how well, diabetes has been diagnosed, and classified into types (e.g., T1D, T2D, diabetes in pregnancy). Since the overwhelming majority of adults with newly diagnosed diabetes have T2D, the total incidence remains a very good proxy for the incidence of T2D. On the other hand, changes in diagnostic criteria can have uncertain effects on observed incidence, depending on the rate at which the uptake of such changes has occurred. There is also no measure of undiagnosed diabetes and changes in screening behaviour can confound analysis of secular trends of incidence of clinically diagnosed diabetes. Analysis of secular trends in data sources that rely on the use of blood glucose lowering drugs to identify diabetes status can be confounded by changes in prescribing behaviour.

Despite these limitations, the feasibility of using population-based EMRs in measuring prevalence, incidence and secular trends has been demonstrated in some countries/areas with national or territory-wide database, with most of these countries/areas having universal health coverage. The design of these EMRs can serve as a reference for other clinical populations where similar data are not available due to resources or system factors. Panel 3 provides a list of clinical and laboratory measurement for collection at diagnosis and regular intervals (e.g., every 2-3 years) for clinical management and quality assurance purposes. By redesigning workflow and using a team approach to set up registers, we can fill some of these data gaps. By using a unique identifier, these databases can be linked to population statistics collected during census or other government departments such as socio-demographic[492] and meteorological data.[130]

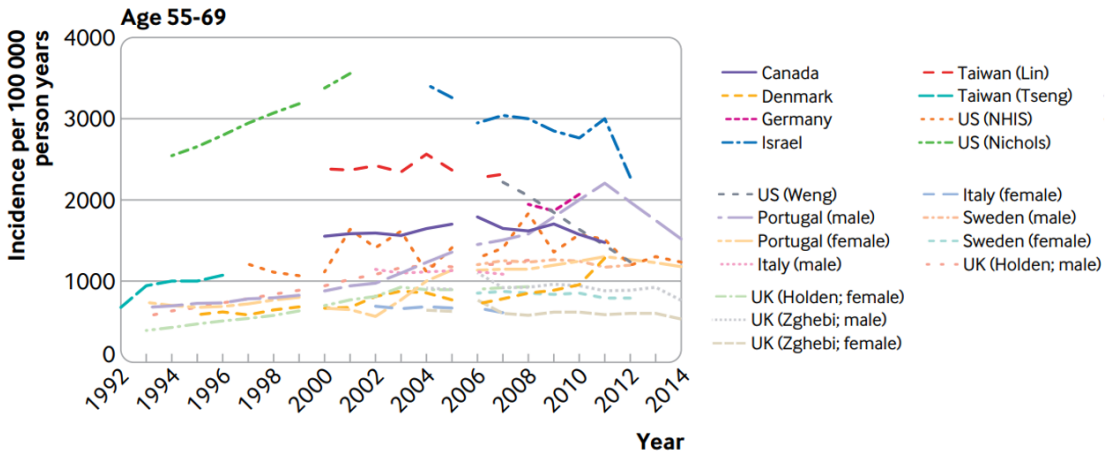
For accounting purposes, there is increasing digitalisation of hospitalisation records and disease registers (cancer, ischaemic heart disease, coronary interventions, heart failure, dialysis, depression).[493] In some countries where establishment of a national diabetes register is not practical, supporting a consortium of diabetes teams to collect data in a structured manner during their routine clinical practice may be an alternative. By combining structured databases with population statistics, EMRs and disease registers, we can identify upstream determinants, uncover treatment gaps, classify patient subgroups, perform analytics and evaluate the effectiveness of medications in real-world practice.[494] In some areas where large-scale RCT data are not available, these databases can be used to verify their effectiveness in real-world practice. For example, in Asia, these databases were used to confirm the benefits of statins in reducing cardiovascular events[495] including peripheral arterial disease[496] and CKD[497] to inform practice, albeit RCTs remain the gold standards. By sharing these best practices and real-world data, we can also perform comparative analysis on diabetes epidemiology and care standards in different populations and settings to advocate for better diabetes management and prevention.[439,498]

### *11.2 EMR and administrative databases suggest declining diabetes incidence in some countries*

Many of these EMRs and registers were established through introduction of quality improvement programmes where care organisation has resulted in structured collection of real-world data which has enabled the systematic analysis of clinical outcomes and effectiveness of interventions.[499] These data availability have also motivated decision-makers to invest in these programmes and increase their impacts.[498] In Israel, analysis of a large insurance group revealed an 18% decline in diabetes incidence during the period 2006–2012.[500] Analysis of claims data in the USA demonstrated a decline of incidence from 1.0% to 0.65% in 2007–2012.[501] Data from the Korean Health Insurance Database showed a decline in incidence in 2005–2009 and a consequent period of stabilisation until 2012.[502] In Hong Kong, while stabilising incidence trend in the middle-aged and falling trend in the elderly were observed between 2001 and 2016, there was significant increase in diabetes incidence in those under the age of 40.[50] Stabilisation of incidence has also been reported using data from a consortium of 11 integrated healthcare delivery systems with EMRs in 10 states of the USA in 2006–2011[503] and that of the Scottish National Register in 2004–2013.[504] In contrast, studies from England and Wales (1994–1998),[505] Portugal (1992–2015)[506] and Canada (1995–2007)[507] reported increases in diabetes incidence.

The first attempt to systematically collate published data on the trends of incidence of diabetes in adults (mainly due to T2D) revealed the majority of the studies came from administrative data sources rather than health surveys. While most studies reported increasing incidence between 1990 and 2005, from 2006–2014, 27% of reported populations had stable incidence over time, while 36% reported a declining trend; only 36% reported an increasing trend in the incidence of diabetes (Figure 20). The studies predominantly came from HICs, and trends may be different in LMICs. Furthermore, most studies could not determine the difference between a true fall in incidence and a change in diagnostic and screening behaviour.[508] Nevertheless, these encouraging trends are in contrast to the rising prevalence as reported as the main index in most analyses. With increasing popularity and adoption of EMRs and data digitalisation in high- and middle-income countries, many of which are undergoing major healthcare reforms, the use of administrative databases to define incidence and prevalence has become increasingly feasible.

**Figure 20. A systematic review showing the trends of annual incidence of diabetes during 1992-2014 among people aged 55-69. Most of the declining trends occur in high-income countries (HICs) with paucity of information in low- and middle-income countries. These data highlight the importance of societal determinants where key upstream factors notably, better education system, good governance and social policies in HICs may underline these favorable trends, calling for both population and individual-based strategies for prevention and control of diabetes and NCD (Magliano DJ et al, BMJ 2019).**




### *11.3 Use data analytics to practise precision medicine and discover new knowledge*

By creating these registers, EMR, population statistics, health surveys and cohort analysis, researchers can start to identify the linkage between causes, interventions and outcomes, based on which, algorithms and models can be developed for cross-validation as demonstrated in our case study using China as an example. These context-relevant models/algorithms can be used to prioritise interventions and identify patient subgroups who can be matched to different strategies, in order 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.[473]

## 12 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 RCTs. We have highlighted the utility of using structured data collection through quality improvement programmes to improve care standards and monitor clinical outcomes. Where such structured data are available, we were able to demonstrate the declining trends of incidence of diabetes and its complications in these populations. Through these databases, we also observed emerging trends and unmet needs in subpopulations. Apart from the multiple morbidities including frailty, depression and cognitive decline associated with ageing and long disease duration, the high event and death rates in YOD 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 healthcare barriers in many subpopulations, notably the migrant, minor ethnicity and underserved populations, in many HICs. Given the lifecourse 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. In order to implement what we have learnt and created to benefit those with or at risk of having diabetes and to make our healthcare sustainable, there is an urgent need to re-organise care by training non-physician personnel and use a team approach, assisted by ICT, to deliver data-driven integrated care to empower self-management and reduce multiple risk factors. To achieve this system change, alignment amongst payers, planners and providers are needed to address the pluralistic needs of patients. Meanwhile, additional research are needed to understand patient-important outcomes including values and preferences as well as psychosocial and cultural factors which influence lifestyle, self-management and health-seeking behaviours.

While globalisation has uplifted the living standards in many people living in LMICs, it has also dramatically changed the ecosystem and human behaviours, especially in many emerging economies. In these countries/areas hit hardest by the epidemic, the ill-prepared healthcare system, lack of capacity and insufficient data to guide actions have led to the majority of affected people not diagnosed, treated or controlled. Yet, examples from both HICs and LMICs have demonstrated that by implementing a society-community-individual strategy, we can potentially reduce the impacts of diabetes and other NCDs by creating a health-enabling environment and strengthening the healthcare 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 to many NCDs. This is a high calling which concerns all of us as global citizens who have contributed to this ecosystem, one way or another, to fuel the epidemic and as such, have the collective responsibilities to rise to this grand challenge to sustain our environment and use our finite resources wisely to preserve humanity.

## Author Contributions

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## Declaration of interest


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**Panel 1. Levels of care in type 1 diabetes in children and young adults, developed by the Life for a Child Programme.[392]**

| Tier | Level of priority | Insulin | Blood glucose monitoring | $HbA_{1c}$ | Complications screening | Diabetes education | Inter-clinic range of clinic mean A1c | Mortality and Complications |
|---|---|---|---|---|---|---|---|---|
| **Minimal care** | 1A | Human insulin, premixed insulin only, once to twice daily injections | Only at clinic | None | None/just weight | Minimal or no diabetes education. Care from general physician or paediatrician. | 12-14+% (108-130 mmol/mol) | High mortality from misdiagnosis and acute complications. Serious early-onset long-term complications very common in survivors. |
| | 1B | Human premixed insulin only, twice daily injections | 1-2 tests/day | Done in laboratory or 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% (80-108 mmol/mol) | Substantial mortality, serious early-onset long-term complications common. |
| | 1C | Human insulin, short- and long-acting, twice daily injections | | | | | 9-10.5% (75-91 mmol/mol) | |
| **Intermediate care** | 2A | Human insulin, multiple daily injections ("basal-bolus regimen") | 2-3 tests/day | 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, + dietitian and social worker if possible. Diabetes camps. Peer & school support, 24-hour emergency call service. | 8-9.5% (64-80 mmol/mol) | Infrequent mortality, serious long-term complications rare unless less-than-optimal blood glucose control. |
| | 2B | Human insulin, multiple daily injections +/- insulin pens | 4+ tests/day | | | | | |
| **Comprehensive care** | 3A | Insulin analogues ("basal-bolus regimen") with insulin pens | 5+ tests/day | Point-of-care | Full complications screening including all above + fundus photography, thyroid, coeliac (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 & school support, 24-hour emergency call service. | 6.5-8.5% (48-69 mmol/mol) | Mortality very rare, long-term complications long-delayed or prevented entirely except if blood glucose control is suboptimal. |
| | 3B | Insulin pump + consumables | | | | | | |
| | 3C | Insulin pump + consumables | Continuous glucose monitoring (CGM) + consumables | | | | | |
| | 3D | Artificial pancreas + consumables CGM + consumables | | | | | | |

**Panel 2. Delivery of a basic type 2 diabetes care plan using a nurse-healthcare 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.**

| Facilities, equipment and procedures | |
|---|---|
| No of patients | 800 patients depending on case mix |
| Workforce | 1 nurse and 1 healthcare assistant under medical supervision |
| Space | 200-300 square feet with basic office equipment (computer, email, telephone, fax, photocopying machines) for assessment and group education away from busy wards and clinics |
| Assessment tools | Monofilament and tuning fork (sensory neuropathy)<br>Hand-held ophthalmoscope or fundus camera (retinopathy)<br>Blood tests (plasma glucose, $HbA_{1c}$, lipids, renal/liver function, estimated glomerular filtration rate, uric acids, haematology)<br>Urine tests (urinary albumin:creatinine ratio) |
| Education tools | Charts and materials to explain nature of diabetes (causes/consequences), plan of follow-up (how often and by whom), self-monitoring (nature, how often) and treatment targets ($HbA_{1c}$, BP, LDL-cholesterol and body weight), syringes, insulin pens, monitoring devices for demonstration |
| Assessment items | Structured form for collection of age, sex, duration of diabetes, education, occupation, tobacco/alcohol intake, family history, self-care, feet (skin, nerves and blood vessels) and eye (visual acuity, cataract, retinopathy, history of laser or surgery), past history of medical illness (notably hospitalisations due to coronary heart disease, stroke, cancer, lower extremity amputation), major operations/procedures and significant symptoms (e.g., erectile dysfunction) |
| Computer database | Data collection for audit and recall purpose<br>Use risk equations to estimate future risk of events with simple to read report and decision support depending on availability and support |
| Frequency of assessment | Baseline assessment followed by 6–9 months with more frequent follow-up for education, reinforcement and treatment adjustment<br>Repeat assessment at 12 months to review progress and every 24–36 months with 4–6 monthly review once stable |
| Other activities | Group education, individual education, teaching of techniques, other classes on diet, physical activity, stress management, screening of family members and high-risk individuals (e.g., polycystic ovary syndrome, gestational diabetes, family members) and peer support depending on availability of resources |

| **Number of patients who can be served using a doctor-nurse-healthcare assistant team during a typical week** | | | | | |
|---|---|---|---|---|---|
| | Monday | Tuesday | Wednesday | Thursday | Friday |
| Morning session (4 hours) | | | | | |
| Structured assessment (~1 hour) and data entry | 3-4 patients | 3-4 patients | 3-4 patients | 3-4 patients | 3-4 patients |
| Afternoon session (4 hours) | | | | | |
| Group education by nurses (~45-mins) | 10 patients | | 10 patients | | 10 patients |
| Nurse/healthcare assistant support (manage register, phone counselling, patient reminder, urgent issues) | ✓ | ✓ | ✓ | ✓ | ✓ |

| **A flow chart showing the utilisation of person-hours to provide a structured, integrated assessment, education and supporting service over one year** | |
|---|---|
| Person-hours available | 8 working hours/day × 5 days/week × 48 weeks × 2 staff = 3,840 hours |
| Person-hours required | <u>Structured assessment at baseline and 1 year later (~1 hour each)</u><br>800 patients × 2 hours = 1,600 hours |
| Person-hours required | <u>Group education at baseline and 1 year later (~45-mins each)</u><br>800 patients × 1.5 hours = 1,200 hours |
| Person-hours remaining | <u>Provision of nurse/healthcare assistant support</u><br>1,040 hours |

**Panel 3. Recommended list of data for establishment of a diabetes register for risk stratification, clinical management and monitoring purpose. The fields highlighted in bold/italic represent a minimal dataset in less-resourced settings which should be documented at presentation and every 12-24 months, as appropriate. A validated risk stratification programme based on different combinations of these risk factors and complications was included as an example.**

| History taking | Clinical assessments | Laboratory tests |
|---|---|---|
| ***Year of assessment*** | ***Blood pressure*** | ***Fasting plasma glucose*** |
| ***Date of birth/age*** | Pulse rate | ***$HbA_{1c}$*** |
| ***Sex*** | ***Body weight*** | ***Total cholesterol*** |
| ***Year of diagnosis / diabetes duration*** | ***Body height*** | HDL-cholesterol |
| ***Types of diabetes*** | ***Waist circumference*** | LDL-cholesterol ***(or non-HDL-cholesterol)*** |
| ***Proneness to ketosis*** | ***Visual acuity*** | ***Triglyceride*** |
| Highest education attained | ***Retinopathy (non-proliferative, proliferative, sight-threatening if available)*** | ***Urinary albumin:creatinine ratio*** |
| ***Use of tobacco*** | ***Foot pulses*** | ***Plasma creatinine*** |
| Use of alcohol | Skin abnormalities | ***Estimated glomerular filtration rate (eGFR)*** |
| Family history of diabetes or maternal hyperglycaemia | Foot deformities | Blood haemoglobin |
| Family history of renal failure | ***Sensory neuropathy*** | |
| Family history of premature cardiovascular disease (<60 years) | | |
| Vaccination | | |
| Contraception | | |
| History of gestational diabetes | | |
| **Macrovascular complications** | **Microvascular complications** | **Comorbidities** |
| ***Ischaemic heart disease*** | ***Foot ulcers*** | ***Hyper/hypoglycaemic crisis*** |
| ***Heart failure*** | ***Laser or Eye surgery*** | Severe sepsis or chronic infections (e.g., tuberculosis, hepatitis B and C) |
| ***Stroke*** | ***Renal transplant*** | Any cancer |
| ***Non-traumatic lower extremity amputation (below/above knee)*** | ***Dialysis*** | Depression |
| **Oral glucose lowering drugs** | **Injectables** | **Cardiovascular drugs** |
| ***Metformin*** | ***Insulin*** (brand names, types, regimens and total daily dose) | ***HMG-CoA reductase inhibitors (statins)*** |
| ***Sulfonylurea*** | Insulin analogues (brand names) | ***Renin angiotensin system inhibitors*** |
| Alpha-glucosidase inhibitor | Glucagon-like peptide-1 receptor agonist (dose and regimen) | ***Aspirin*** |

| | | |
|---|---|---|
| | | ***Other BP lowering drugs*** |
| | | ***Other lipid regulating drugs*** |
| Thiazolidinediones | | Other antiplatelet drugs |
| Dipeptidyl peptidase-4 inhibitor | | |
| Sodium-glucose co-transporter 2 inhibitor | | |

**Risk stratification and follow-up actions (adapted from the JADE Programme)[464]**

| | Very High risk | High risk | Medium risk | Low risk |
|---|---|---|---|---|
| Cardiovascular disease and/or end-stage kidney disease | Yes | No | No | No |
| eGFR (ml/min/1.73m$^2$) | Severe (<15 or dialysis) | Moderate (15-60) | Mild (60-90) | Normal (≥90) |
| Other risk parameters | Not applicable | At least 3 | 2 | 0-1 |
| Risk scores for future events* | Very High | High | Moderate | Low |
| Estimated cumulative 5-year cardiovascular-renal event rates | 38% | 18% | 8% | 2% |
| Adjusted hazard ratio (referent group: 1) | 8.6 | 4.7 | 2.8 | 1 |
| Recommendations | 1. Structured comprehensive assessment by trained nurses and healthcare assistants at presentation to identify needs and build patient-provider relationships<br>2. Establish database to set up register and use data to stratify risk, individualise treatment targets and care plan<br>3. Use personalised data to provide feedback to patients and doctors with emphasis on risk profiles, attainment of treatment to multiple targets ($HbA_{1c}$, BP, LDL-cholesterol and body weight), use of statins and RASi and quit smoking<br>4. Use non-physician personnel to educate, empower and engage patients for self-management with social and peer support, as needed<br>5. Arrange early review by team members and adjust treatment strategies and provide support aiming to achieve control in 6–12 months<br>6. Arrange 3–6 monthly reviews by team members once stable<br>7. At least 6–12 monthly reviews even if low risk due to silent deterioration<br>8. Structured comprehensive assessment every 18–24 months for quality assurance especially if infrequent review | | | |
| Risk stratification parameters | 1. Current or ex-smoker<br>2. BMI ≥27.5 kg/m$^2$ or waist circumference ≥80 cm in women or ≥90 cm in men for Asians (ethnic-specific)<br>3. BP>130/80 mmHg or treatment with BP-lowering drugs<br>4. $HbA_{1c}$ >8% (64 mmol/mol)<br>5. LDL-cholesterol >2.5 mmol/L (100 mg/dL) and/or treatment with statins<br>6. TG >2.3 mmol/L (204 mg/dL) and/or HDL-cholesterol <1 mmol/L (39 mg/dL) and/or treatment with fibrates<br>7. Random spot urinary albumin:creatinine ratio >3.5 mg/mmol (women) or >2.5 mg/mmol (men)<br>8. Foot at risk with sensory neuropathy, skin changes (e.g., fungal infection, dry skin) and/or deformities (e.g., claw feet or hallux deformities)<br>9. Any retinopathy | | | |

Footnotes: *Once these registers are established, population-specific risk equations and models can be built to predict absolute event rates which can further improve the performance of the risk stratification programme.

**Table 1. Out-of-pocket (OOP) cost to people with diabetes in selected countries expressed in US dollar per person per year (refer to supplemental material for full reference list)**

| Diabetes type | | Annual total OOP cost per person for diabetes related care | | OOP as % of total diabetes related healthcare cost (%) | OOP as % of personal income or family income (%) | Sources |
|---|---|---|---|---|---|---|
| | | Original estimates, USD (year) | Converted to 2017 USD* | | | |
| **Low-income countries** | | | | | | |
| India | 1 | ~455 (2012) | ~521 | ~87 | ~16 | 1 |
| India | Not specified | ~515–525.5 (2009) | ~652–665 | 98–100 | NA | 2 |
| China | 2 | 596 (2013) | 666 | NA | 5.8 for the high-income household; 32.2 for the low-income household | 3 |
| Pakistan | 2 | ~197 (2006) | ~278 | ~100 | ~18 for the low-income household | 4 |
| Sudan | 1 | ~280 (2004) | ~429 | ~99 | ~23 | 5 |
| Nigeria | 2 | ~1,558 (2013)** | 1,742 | ~100 | NA | 6 |
| **High income countries** | | | | | | |
| USA | Not specified | Privately insured:~1,184 (2013) | ~1324 | Privately insured: ~11 | NA | 7 |
| | | Medicaid: ~260 (2008); Uninsured:~1,119 (2008) | Medicaid: ~339; Uninsured: 1,461 | Medicaid: ~2.7; Uninsured: ~40.4 | | 8 |
| | 1 | Medicare:~542 (2013) | ~606 | NA | NA | 9 |
| | 2 | Medicare:~529 (2013) | ~591 | NA | NA | 9 |
| Canada | 1 | ~808–3,693 (2015) | ~860–3,930 | ~22–81 | ~3–17 | 10 |
| | 2 | ~544–1,440 (2015) | ~579–1,532 | ~36–70 | ~2–9 | 10 |

Footnotes: *Adjusted to 2017 USD using the medical care part of consumer price index (https://www.bls.gov/cpi/data.htm)**. Recalculated by excluding non-medical cost such as transportation and diabetes diet from the original estimates. NA, not applicable.

**Table 2. Summary of evidence of modifiable risk factors and their associated risk of type 2 diabetes (refer to supplemental material for full reference list).**

| Modifiable risk factor category | Risk factor | References | Studies | Number of incident cases | Relative risk estimate |
|---|---|---|---|---|---|
| *Behavioural* | Overall physical activity | Smith et al, Diabetologia 2016[1] | 28 cohorts; 12 NA, 8 Europe, 6 Asia, 2 Australasia | 84,134 | RR 0.87 per 10 MET h/week difference in physical activity |
| | Sedentary behaviour | Wilmot et al, Diabetologia 2012[2] | 9 cohorts; 5 NA, 2 Europe, 2 Australasia | 23,230 | RR 2.12 comparing highest level of sedentary behaviour with least |
| | Fitness–enhancing physical activity | Zaccardi et al, Atherosclerosis 2015[3] | 7 cohorts; 4 NA, 2 Asia, 1 Europe | 8,564 | 0.95 per 1-MET higher baseline CRF |
| | Sleep | Shan et al, Diabetes Care 2015[4] | 10 cohorts; 5 NA, 2 Europe, 2 Asia, 1 Australasia | 18,443 | U-shaped relationship with lowest risk at sleep duration of 7–8 hours per day |
| | Dietary patterns (MD, DASH, AHEI) | Jannasch et al, J Nutr 2017[5] | 16 cohorts | Not specified | RR between extreme quantiles<br>MD 0.87<br>DASH 0.81<br>AHEI 0.79 |
| | Foods<br>Nuts/seeds<br>Whole grains<br>Red meat<br>Processed meat<br>Yoghurt<br>Sugar–sweetened beverages<br>Fibre<br>Glycaemic load | Micha et al, PLoS One 2017[6] | <br>5 cohorts<br>10 cohorts<br>9 cohorts<br>8 cohorts<br>9 cohorts<br>17 cohorts<br><br>5 cohorts<br>17 cohorts | <br>13,308<br>19,791<br>28,228<br>26,256<br>32,995<br>38,253<br><br>3,029<br>46,115 | <br>0.87 per 4s/wk<br>0.88 per 1s/d<br>1.19 per 1s/d<br>1.51 per 1s/d<br>0.82 per 1s/d<br>1.27 per 1s/d<br><br>0.76 per 30g/d<br>1.13 high vs. low<br>**s: serving* |
| | Macro–nutrients (e.g. saturated fat) | de Souza et al, BMJ 2015[7] | 8 cohorts; 4 Europe, 4 NA | 8,739 | Non-significant association RR 0.95 |
| | Micro–nutrients (e.g. vitamin D) | Song et al, Diabetes Care 2013[8] | 21 cohorts | 4,996 | RR high vs. low 0.62 |

| Modifiable risk factor category | Risk factor | References | Studies | Number of incident cases | Relative risk estimate |
|---|---|---|---|---|---|
| | Smoking | Pan et al, Lancet Diabetes Endocrinol 2015[9] | 88 cohorts | 295,446 | RR 1.37 current smokers vs. never-smokers |
| | Alcohol | Knott et al, Diabetes Care 2015[10] | 38 cohorts; 11 NA, 11 Europe, 12 Asia, 4 Australasia | 125,926 | RR 0.82 in those consuming 10–14 g per day vs. abstainers |
| *Social* | Work-related stress | Sui et al, PLoS One 2016[11] | 7 cohorts; 2 NA, 4 Europe, 1 Asia | 5,511 | Non-significant association RR 1.12 job strain vs. no job strain |
| | Depression | Knol et al, Diabetologia 2006[12] | 9 cohorts; 6 NA, 2 Europe, 1 Asia | Not specified | RR 1.37 depression vs. no depression |
| | Education | Agardh et al, Int J Epidemiol 2011[13] | 23 cohorts; 10 NA, 7 Europe, 2 Asia, 1 Middle East, 1 LA, 2 Africa | 21,978 | RR 1.41 high vs. low education |
| *Environmental* | Air pollution | Eze et al, Environ Health Perspect 2015[14] | 5 cohorts; 3 NA, 2 Europe | Not specified | RR 1.10 per 10 $\mu g/m^3$ $PM_{2.5}$ |
| | Food contaminants | Song et al, J Diabetes 2016[15] | 8 cohorts | Not specified | RR highest vs. lowest concentration: 1.91 dioxin, 2.39 total PCBs, 2.30 chlorinated pesticides |
| *Developmental* | Birth weight | Mi et al, Exp Ther Med 2017[16] | 8 cohorts; 3 NA, 4 Europe, 1 Asia | 3,892 | RR 1.55 low birth weight (<2500g) vs. normal |
| | Breast feeding | Horta et al, Acta Paediatr 2015[17] | 11 cohorts: Not specified | Not specified | RR 0.65 breast feeding vs. not |
| | Age at puberty | Janghorlani et al, Acta Diabetol 2014[18] | 10 studies; 3 Europe, 5 NA, 2 Asia | 22,085 | RR low age at menarche 1.22 vs. average age. |

Footnotes: AHEI, Alternative Healthy Eating Index; CRF, cardiorespiratory fitness; DASH, Dietary Approaches to Stop Hypertension; LA, Latin America; MD, Mediterranean diet; MET, metabolic equivalent of task; NA, North America; PCBs, polychlorinated biphenyls; $PM_{2.5}$, particulate matter ≤2.5μm in diameter; RR, relative risk.

**Table 3. A list of consensus recommendations by members of the Commission adapted from the 'best buys' of the World Health Organization (WHO),[327] United Nations Sustainable Development Goals[399] and WHO Convention Framework for Control of Tobacco[393] of potential interventions that could be employed as part of an integrated approach to type 2 diabetes prevention through government leadership, inter-sectoral collaborations and community mobilisation.**

| | | |
|---|---|---|
| **Educational policies at all levels to improve literacy, self-management and lifelong coping skills** | | |
| **Environmental policies to build 'smoke-free' healthy cities with clean air, water and foods** | | |
| **Social policies to reduce poverty and inequalities and ensure care equity** | | |
| | **Diet** | **Physical activity** |
| **Supranational** | • International trade agreements on food and food-related commodities.<br>• International trade agreements on agriculture. | • International trade agreements on automotive industry.<br>• International agreements on climate change. |
| **National** | • Taxes on less healthy foods levied on producers or consumers; subsidies on healthier foods.<br>• Reformulation of commercially produced food to reduce density of less healthful nutrients.<br>• Restriction of marketing of less healthy foods on television and online.<br>• Mandatory food labelling of nutrients and calories on packaging and menus.<br>• Mandatory restriction of marketing of less healthy foods within stores (e.g., price promotions, placement, volume discounts).<br>• Industry-led reduction in portion size for packaged food and food served ready to eat. | • Taxes on transport mode (e.g., fuel duty).<br>• Subsidies to promote healthy travel (e.g., bike-to-work schemes and subsidised public transport). |
| **Regional** | • Regional school food policies (e.g., breakfast programmes, food and nutrition standards).<br>• Healthy food policies in other publicly-funded spaces (e.g., recreational settings, hospitals, government employers).<br>• Regional social marketing, mass media campaigns. | • School sports funding/organisation - school sports partnerships.<br>• Regional taxes or subsidies on transport mode.<br>• Regional social marketing, mass media campaigns. |

| Educational policies at all levels to improve literacy, self-management and lifelong coping skills | | |
|---|---|---|
| **Environmental policies to build 'smoke-free' healthy cities with clean air, water and foods** | | |
| **Social policies to reduce poverty and inequalities and ensure care equity** | | |
| | **Diet** | **Physical activity** |
| **Local** | • Local restrictions of marketing of less healthy foods in schools, outdoors and in recreational settings.<br>• Use of planning system to regulate food outlets selling/serving food of differential healthfulness. | • Promotion of walking and cycling infrastructure.<br>• Development of local space for physical activity (e.g., parks, leisure centres, playing fields).<br>• Use of local planning regulation to promote walkable neighbourhoods.<br>• Use of local fiscal levers to promote healthy travel (e.g., subsidised public transport, parking charges and congestion charging).<br>• School-based physical activity promotion programmes. |
| **Community** | • Faith-based organisations cooking/food interventions. | • Faith-based organisations physical activity interventions. |
| **Individual** | • Individual, group or digital dietary interventions. | • Individual, group or digital physical activity interventions. |

**Table 4. Major randomised primary prevention studies in type 2 diabetes (refer to supplemental text for full reference list).**

| Study (Year) | Country | Number of participants | Intervention | Duration of follow-up | Relative risk reduction (%) |
|---|---|---|---|---|---|
| Da Qing Diabetes Prevention Study (1997) CDQDPS[1] | China | 577 | Lifestyle modification | 6 years | Diet: 31.0 Exercise: 46.0 Diet-plus-exercise (D+E): 42.0 |
| Da Qing Diabetes Prevention Extended Study (2008) CDQDPS[2] | | | | 20 years | 43.0 (D+E) |
| Da Qing Diabetes Prevention Extended Study (2014) CDQDPS[3] | | | | 23 years | 45.0 (D+E) |
| Diabetes Prevention Study (2001)[4] | Finland | 522 | Lifestyle modification | 3.2 years | 58.0 |
| Diabetes Prevention Extended Study (2013)[5] | | | | 13 years | 38.0 |
| Diabetes Prevention Program (2002)[6] | USA | 3,234 | Lifestyle modification, Metformin | 2.8 years | Lifestyle 58.0; Metformin 31.0 |
| Diabetes Prevention Program Outcome Study (2009)[7] | | | | 10 years | Lifestyle 34.0; Metformin 18.0 |
| Diabetes Prevention Program Outcome Study (2015)[8] | | | | 15 years | Lifestyle 27.0; Metformin 18.0 |
| Prevention of type 2 diabetes by lifestyle intervention (2005)[9] | Japan | 458 | Lifestyle modification | 4 years | 67.4 |
| Indian Diabetes Prevention Programme-1 (2006)[10] | India | 531 | Lifestyle modification; Metformin | 2.5 years | Lifestyle 28.5 Metformin 26.4 |
| Indian Diabetes Prevention Programme-2 (2009)[11] | India | 407 | Lifestyle modification plus Pioglitazone | 3 years | No benefit by adding pioglitazone |
| Zensharen Study for Prevention of Lifestyle Diseases (2011)[12] | Japan | 641 | Lifestyle modification | 3 years | 44.0 |
| Indian SMS Study (2013)[13] | India | 537 | Lifestyle modification | 2 years | 36.0 |

| Study (Year) | Country | Number of participants | Intervention | Duration of follow-up | Relative risk reduction (%) |
|---|---|---|---|---|---|
| Diabetes Community Lifestyle Improvement Programme (2016) (D-CLIP)[14] | India | 578 | Lifestyle modification plus stepwise addition of metformin (for those at highest risk of conversion to diabetes) | 3 years | 32.0 |

**Table 5. Demographic and organisational factors that influence type 2 diabetes prevention policies with contrast between Jamaica[407] and England[509]**

| | Country | | |
|---|---|---|---|
| | | **Jamaica** | **England** |
| Country demographics and healthcare | Total adult population (1000s) | 2,881 | 65,640 |
| | GDP per capital, purchasing power parity (current international dollar) | 8,835 | 42,609 |
| | Total healthcare expenditure (THE) of GDP (%) per capita (USD) | 5.4/266 | 9.1/3,935 |
| | General government health expenditure (% of total health expenditure) | 52 | 83 |
| | Density of physicians (total number per 1,000 population) | 0.4 | 2.8 |
| | Density of nursing and midwifery personnel (total number per 1,000 population) | 1.1 | 8.4 |
| Current burden of disease | Prevalence of diabetes in women/men (%) | 14.4 (7.8–23.3)/ 9.3 (4.5–16.0) | 4.9 (3.1–7.4)/ 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 2025 in women/men (%) | 21.6 (7.2–49.8)/ 13.7 (3.7–33.8) | 5.4 (2.1–11.6)/ 7.8 (3.1–15.9) |
| Current prevalence of risk factors | Prevalence of high blood pressure in women/men (%) | 19.2 (12.0–27.7)/ 24.5 (15.6–34.8) | 12.4 (9.0–16.1)/ 17.9 (13.0–23.2) |
| | Prevalence of overweight and obese in women/men (%) | 63.4 (56.5–70.0)/ 48.3 (41.0–55.4) | 58.5 (53.8–63.0)/ 67.7 (63.3–72.0) |
| | Prevalence of obesity in women/men (%) | 33.0 (25.7–40.0) / 15.19 (10.0–21.2) | 28.3 (24.2–32.5)/ 26.2 (22.1–30.5) |
| Future prevalence of risk factors | Estimated prevalence of obesity in 2025 in women/men (%) | 43.2 (29.5–59.1) / 25.7 (13.2–43.6) | 37.6 (28.7–47.7)/ 37.8 (27.7–49.9) |
| Quality of diabetic care | People with diabetes with $HbA_{1c}$/ fasting blood glucose within target range (%) | 43 | 65.7 |
| | People with diabetes with lipids under control | No population based data | 77.1 |
| | People with diabetes with BP <140/90 mmHg (%) | 16 – 94 % | 73.6 |
| | Diabetes register | Yes | Yes |
| 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 |
| | Insulin available in the public sector | Yes | Yes |

| | Country | | |
|---|---|---|---|
| | | **Jamaica** | **England** |
| Current available treatments | Metformin available in the public sector | Yes | Yes |
| | Statin available in 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 | 2016 first wave of NHS Diabetes Prevention Programme covering 26 million people |

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Figure

**Figure 1. Crude hospitalisation rates (bed-days per 1000 patient-years) for selected principal diagnoses, by attained age, among persons with young-onset type 2 diabetes in the Hong Kong Diabetes Register showing the excess burden of hospitalisation and mental illness (Ke C et al Ann Int Med 2019).**

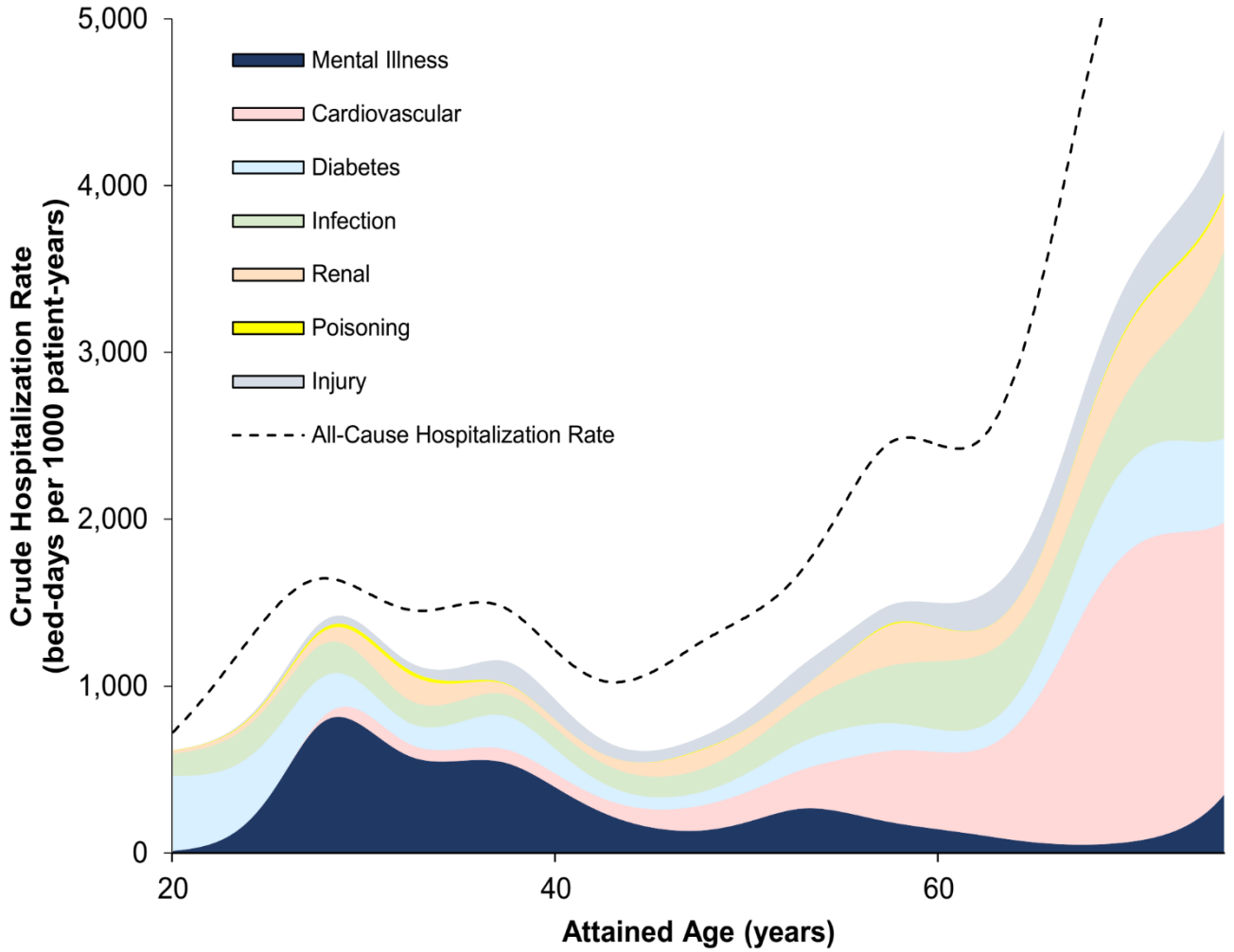


**Figure 2. Standardised rate ratio (SRR) for all-cause mortality for people with diabetes compared to the general population, according to age and countries (refer to supplemental text for details of references).**

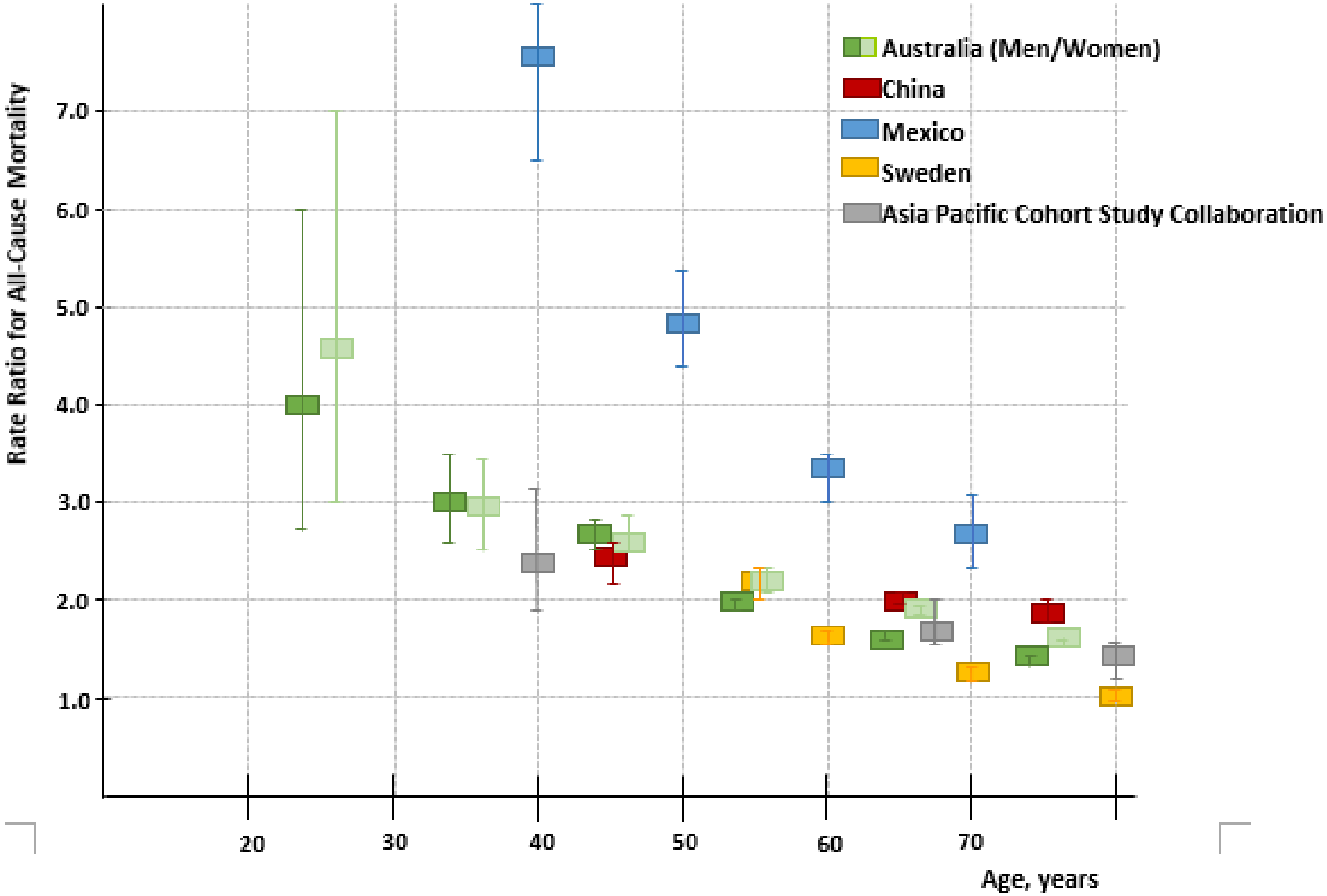


**Figure 3. Lifecourse development of type 2 diabetes, highlighting the role of different risk factors at different stages of the lifecourse. Adolescent obesity and maternal hyperglycaemia are some of the factors that contribute to risk in the next generation, and perpetuating the rising prevalence of young onset diabetes. There are numerous opportunities for prevention and intervention during the lifecourse. The red curved arrow linking different generations represent a combination of different effects including the effects of maternal hyperglycaemia and obesity (directly via modulating growth as well as through epigenetic mechanisms), altered microbiome, as well as shared genetics and behaviour, environmental exposures (Ma RC and Popkin BM PLoS Med 2017).**

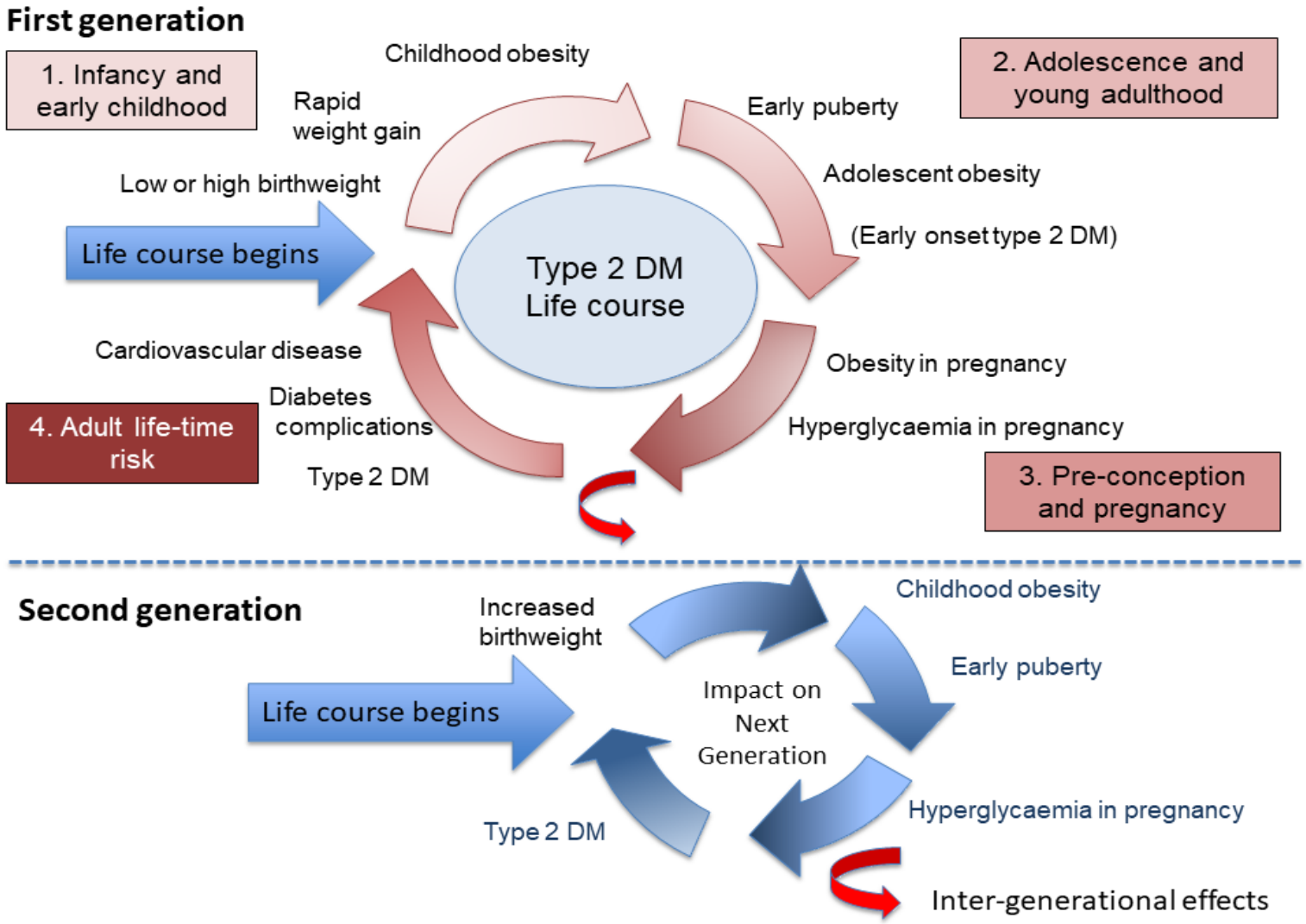


**Figure 4: The environment-lifestyle-host interactions underlie the complex nature of diabetes and NCD which requires a combination of personal and societal strategies by using context-relevant policies and system change in order to cover the full spectrum of health promotion, prevention, treatment, rehabilitation, and social care (refer to Table 1 and section 7.1).**

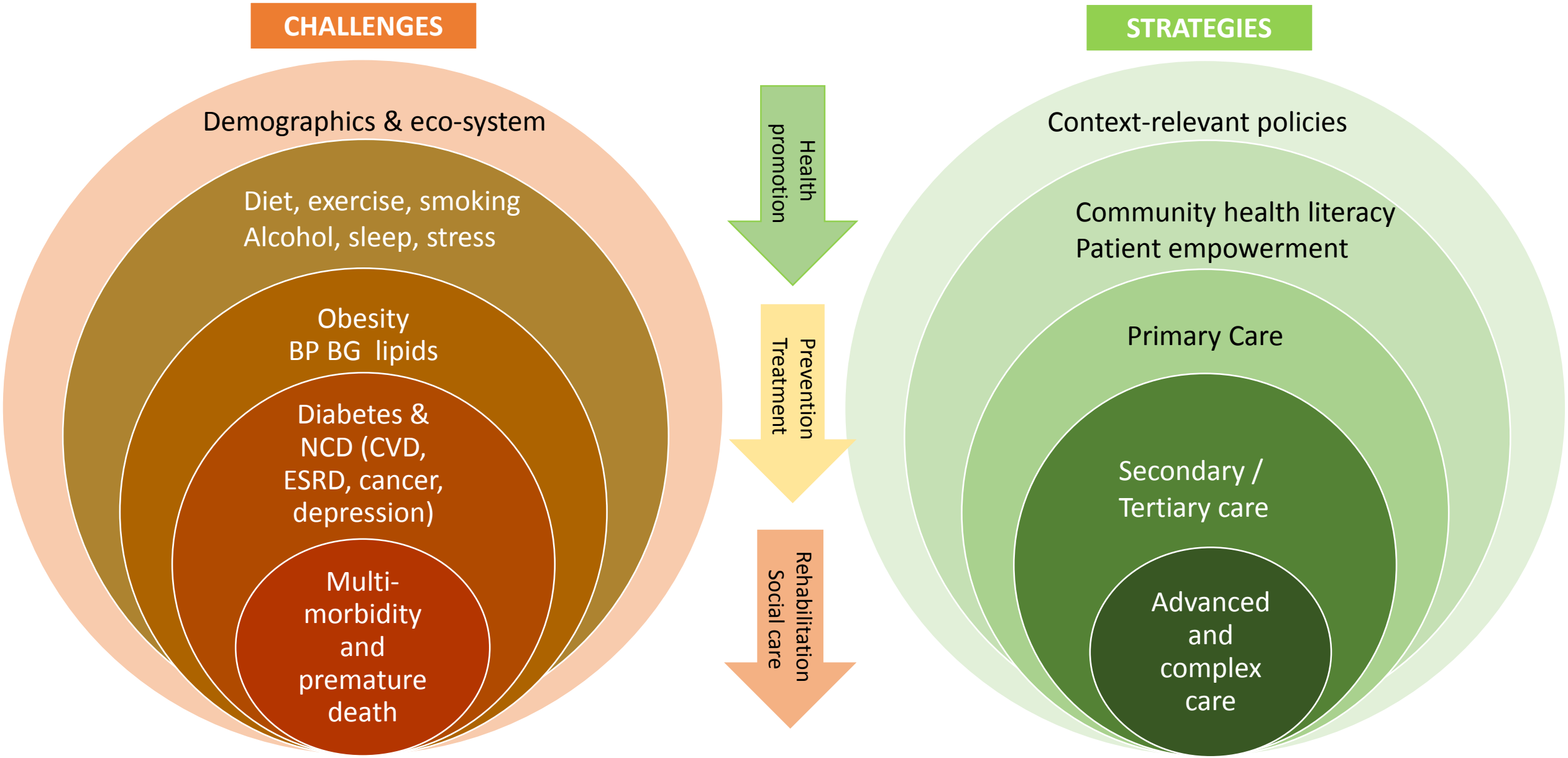


**Figure 5A. Cumulative incidence of diabetes-related complications and related death within the examined Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort of childhood-onset type 1 diabetes, according to calendar year of diagnosis. The p values highlight the lack of improvement of these trends within each age group diagnosed during different time periods.**

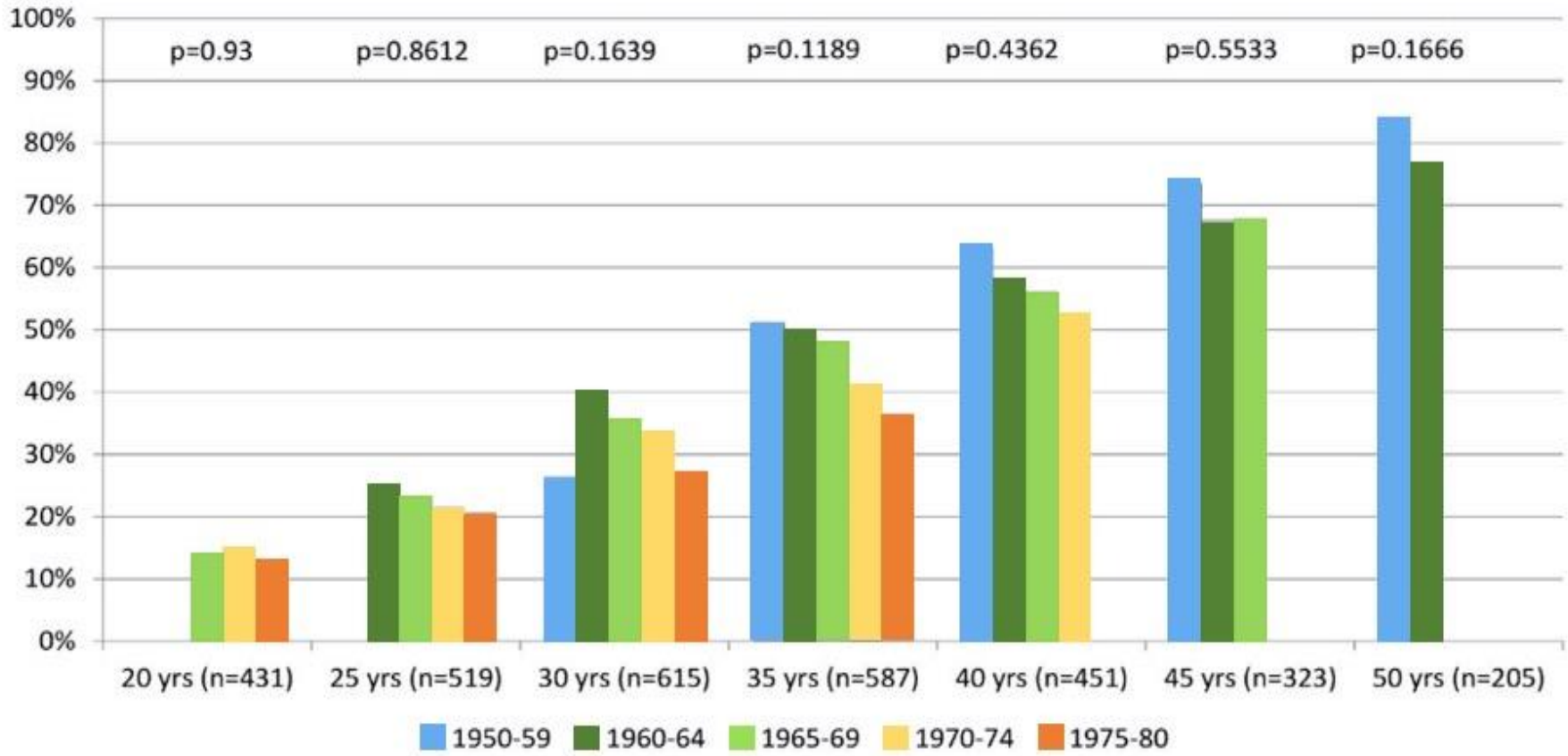
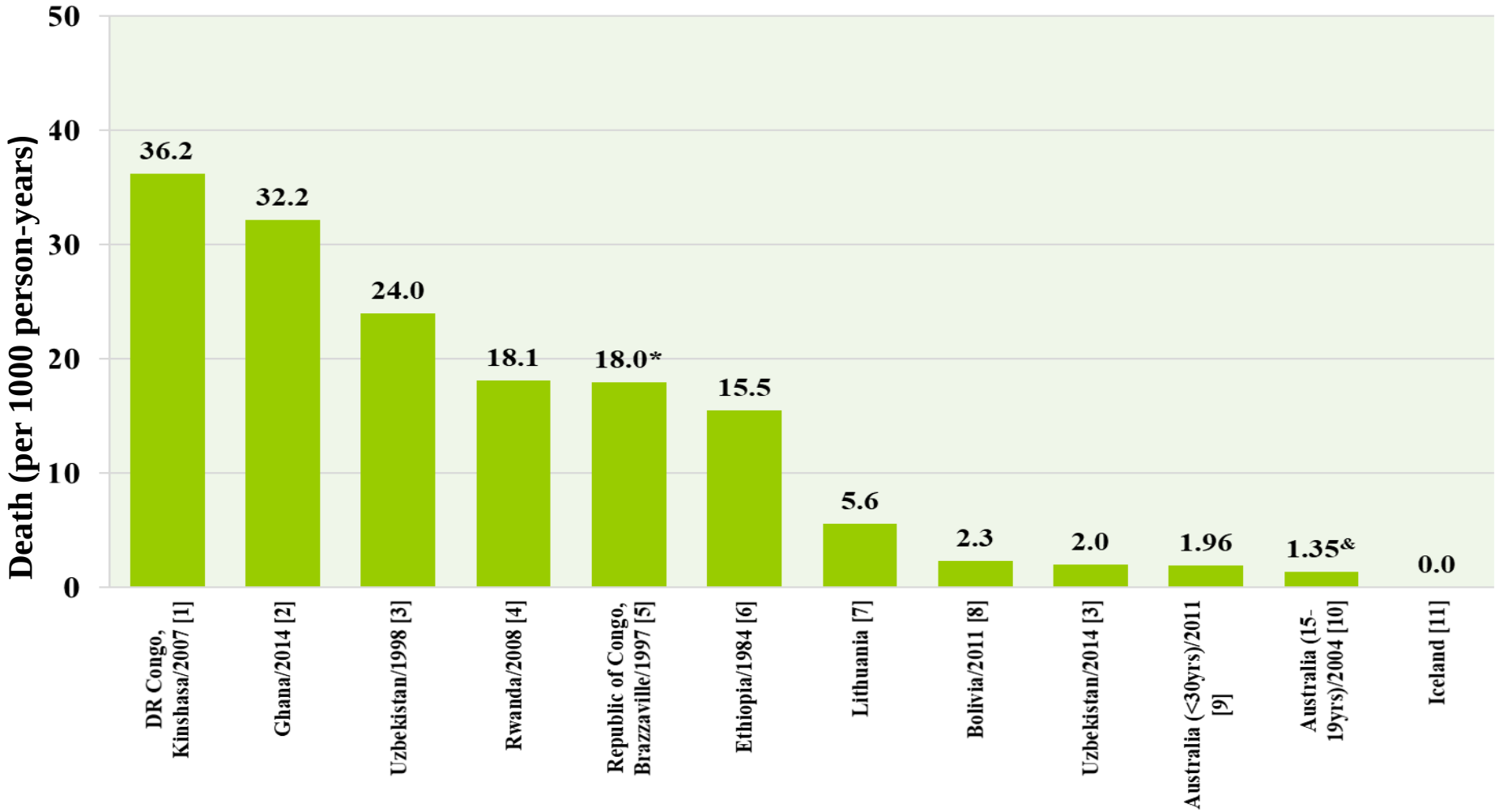


**Figure 5B. Premature death in patients with type 1 diabetes diagnosed before the age of 40 years in different countries (refer to supplemental text for details of references).**




*Onset-DKA related death only
&mean of men and women rates

**Figure 6. A global landscape of $HbA_{1c}$ in 1.9 million people with type 1 or type 2 diabetes reported in more than 20 cohorts with at least 5000 patients per cohort showing high levels of $HbA_{1c}$ especially in patients with type 1 diabetes and young-onset type 2 diabetes (refer to supplemental text for details of references).**

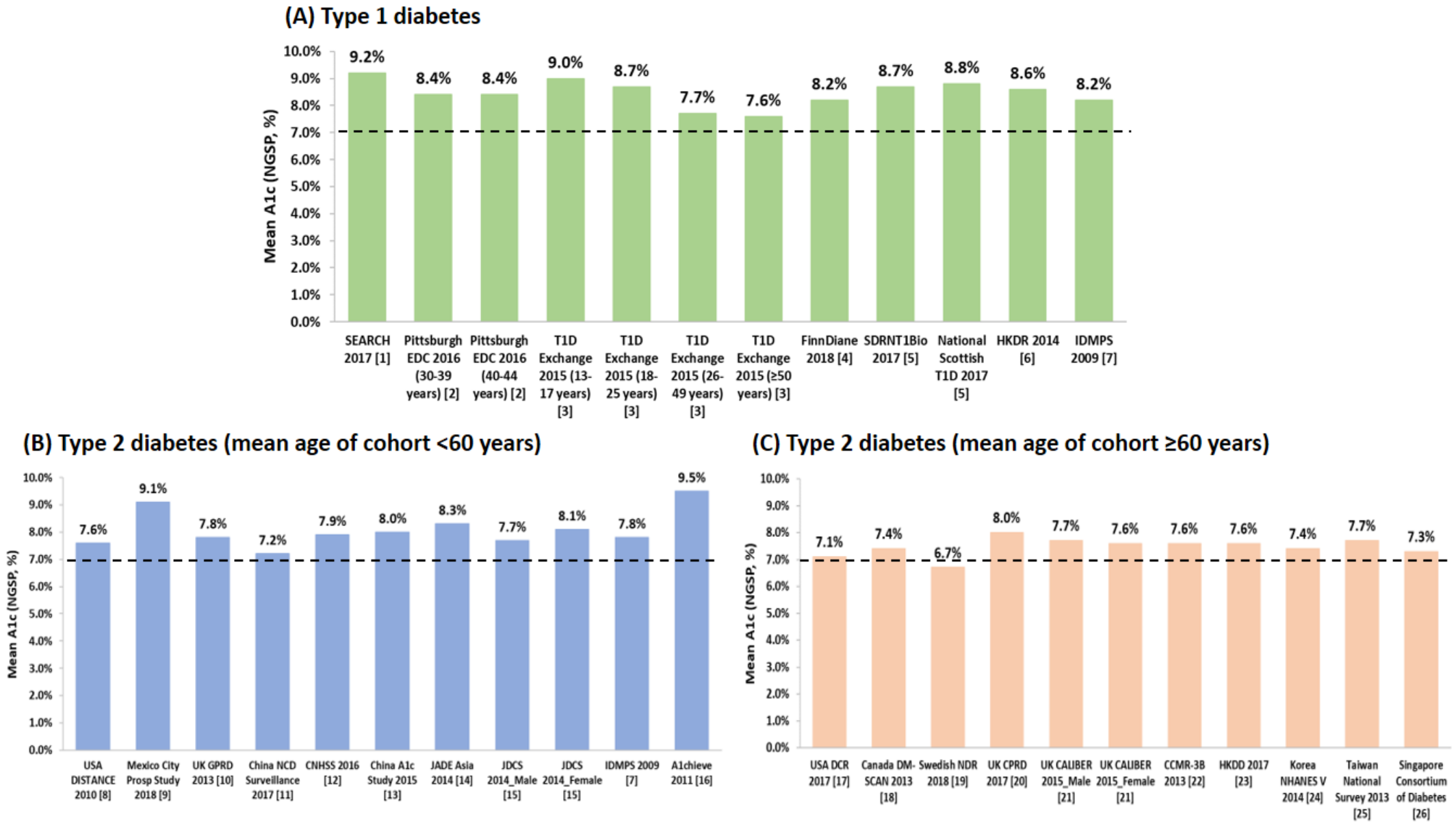


**Figure 7. Trends in all-cause mortality among people with diabetes between 1988 and 2015, by country/region. Note these data are from HICs, showing a paucity of similar data in LMICs (Harding JL et al. Diabetologia 2018).**

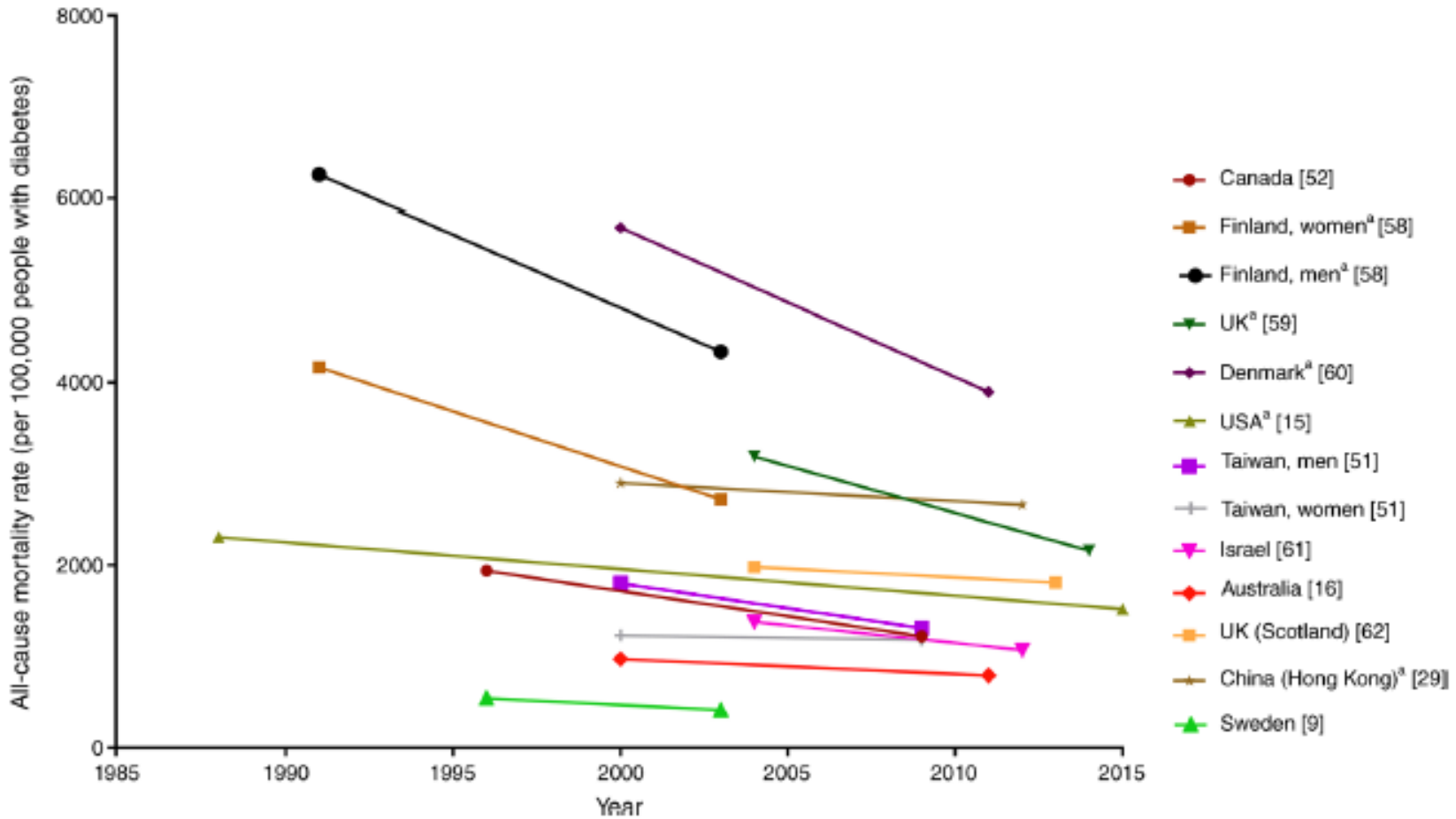
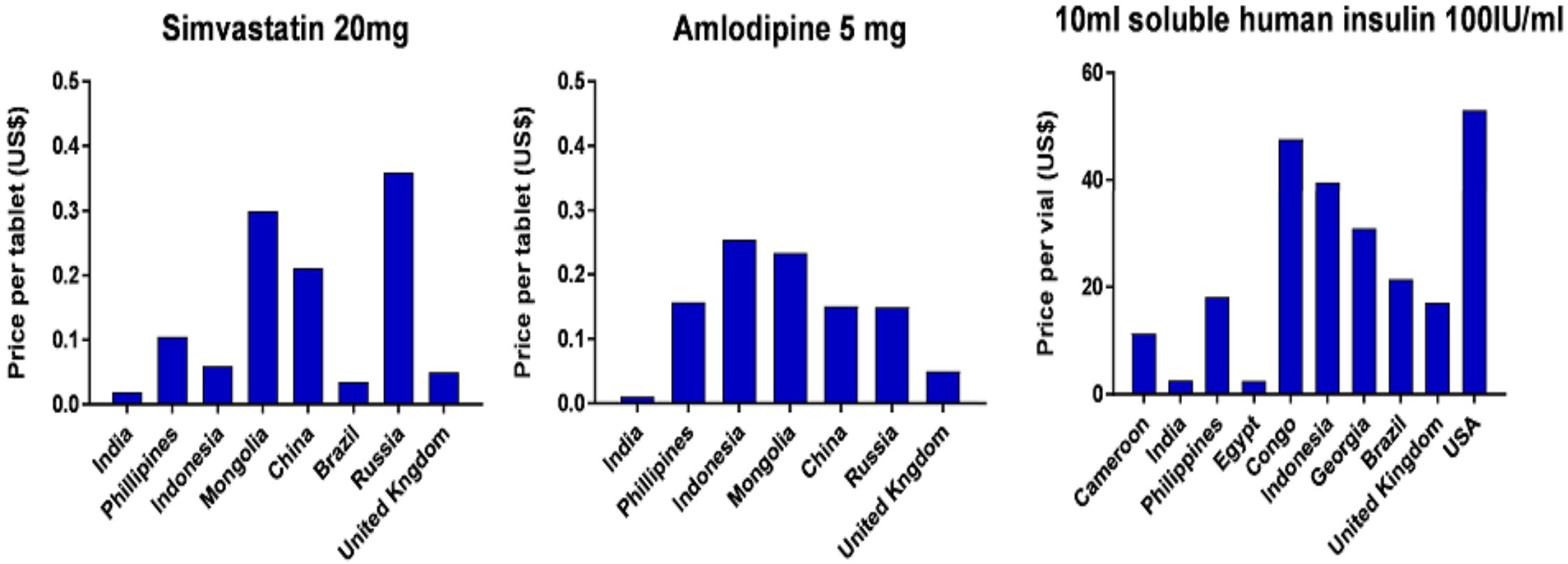


**Figure 8: Price differences in common medications used in patients with diabetes in countries ranked based on gross domestic product per capita in 2011. Prices of simvastatin and amlodipine are pubic sector procurement prices from various surveys conducted by WHO/Health Action International Project on Medicine Prices and Availability between 2002 and 2013. United Kingdom drug prices are based on Category M price. Insulin data are private prices based on a global snapshot on 11 May 2010 as reported by WHO/Health Action International Project on Medicine and Availability.**




World Health Organization. WHO/Health Action International Project on Medicine Prices and Availability http://www.who.int/medicines/areas/access/Medicine_Prices_and_Availability/en/WHO/Health (Accessed o 1 Jan 2018).

**Figure 9. Routes to the translation of evidence into action in clinical and public health interventions (Ogilvie D et al *J Epidemiol Community Health* 2020).**

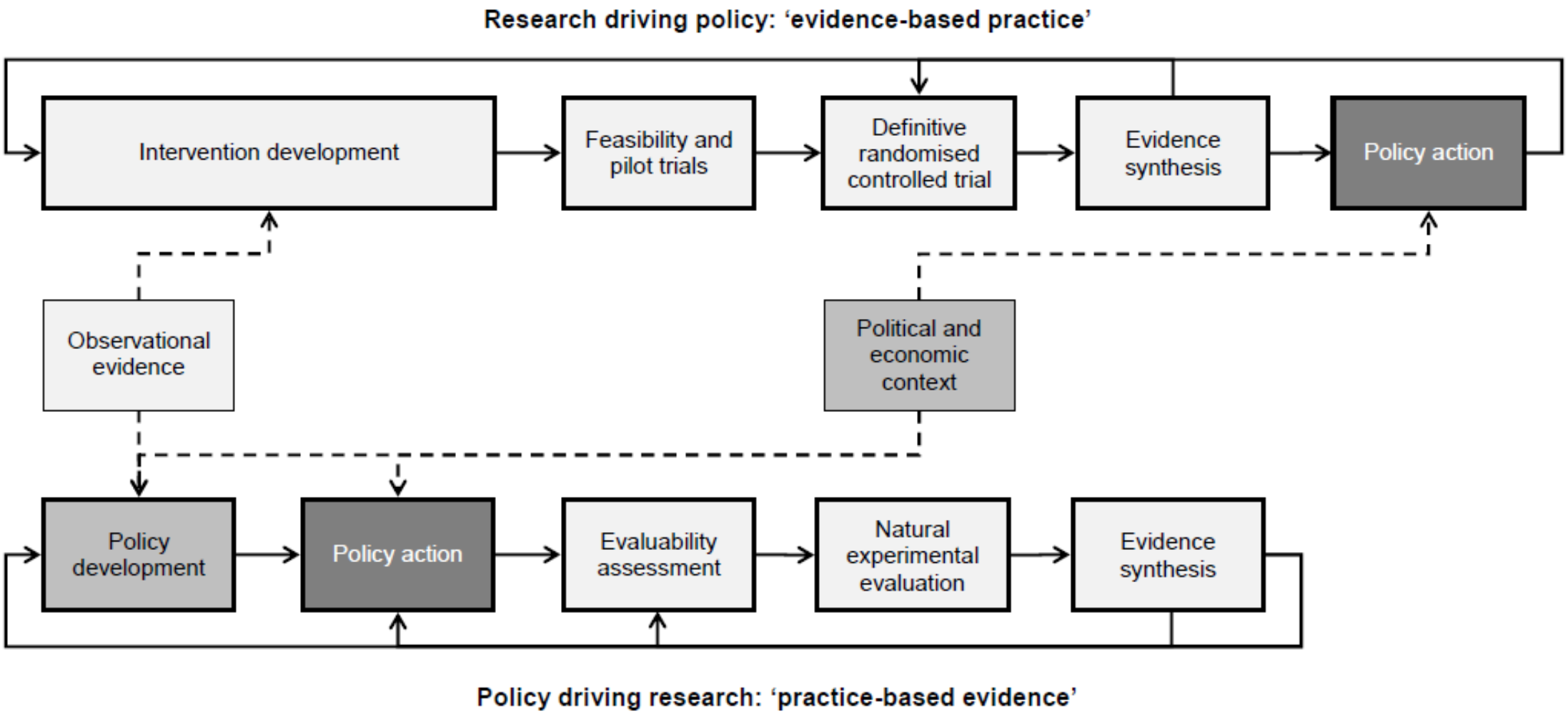
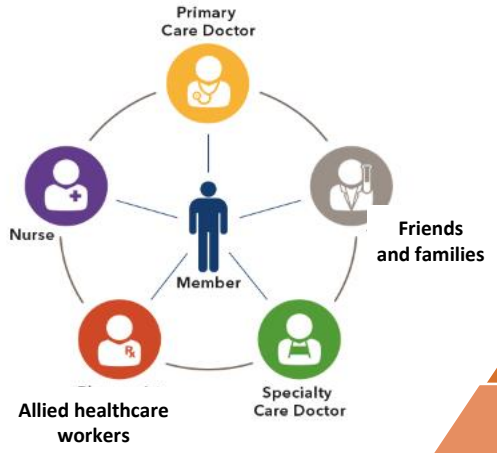


**Figure 10. A conceptual framework for a multicomponent society-community-individual strategy to integrate primary and secondary prevention supported by health and inter-sectoral policies including universal health coverage (UHC), preschool/school education and social/environment protection in line with the United Nations Sustainable Developmental Goals (UN- SDG), WHO NCD Global Monitoring Framework, WHO Framework Convention for Tobacco Control (FCTC) and professional practice guidelines.**





**Individual-based,** integrated care using teams

Team-based integrated care
Prevent diabetes-related complications
(Professional practice guidelines)

**Community-based T2D prevention program** (lifestyle changes and use of metformin), health policies (e.g., tobacco, sugar-sweetened beverages, trans fat) and UHC

Healthy and active lifestyles
Prevent type 2 diabetes
(WHO NCD Global Monitoring Framework and WHO FCTC)

**Society-based** inter-sectoral policies to protect environment, reduce social disparity and improve preschool and school education

Healthy environment
Prevent NCD
(UN-SDG)

**Figure 11. A meta–analysis of 181 trials showing the effects of different quality improvement strategies targeted at patients, providers and systems on $HbA_{1c}$ (NGSP %) in patients with type 2 diabetes (n=135,112) receiving multicomponent integrated care versus usual care. Team change, facilitated patient relay and patient education/self management have the largest effect size, expressed as mean difference (MD) with 95% confidence interval (CI). Similar changes are also reported for blood pressure and LDL-cholesterol. *N* is the number of trials (Lim LL et al Diabetes Care 2018).**

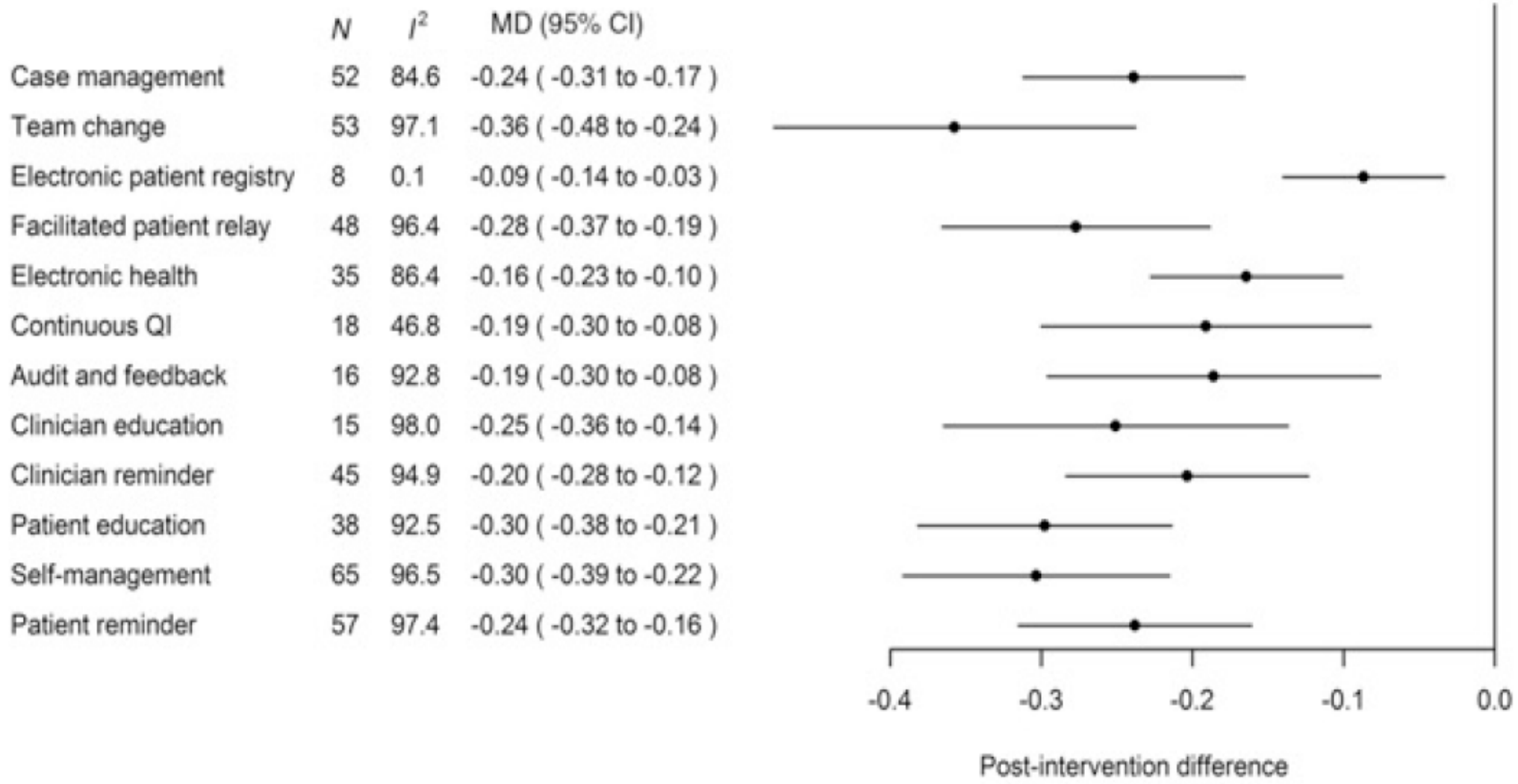
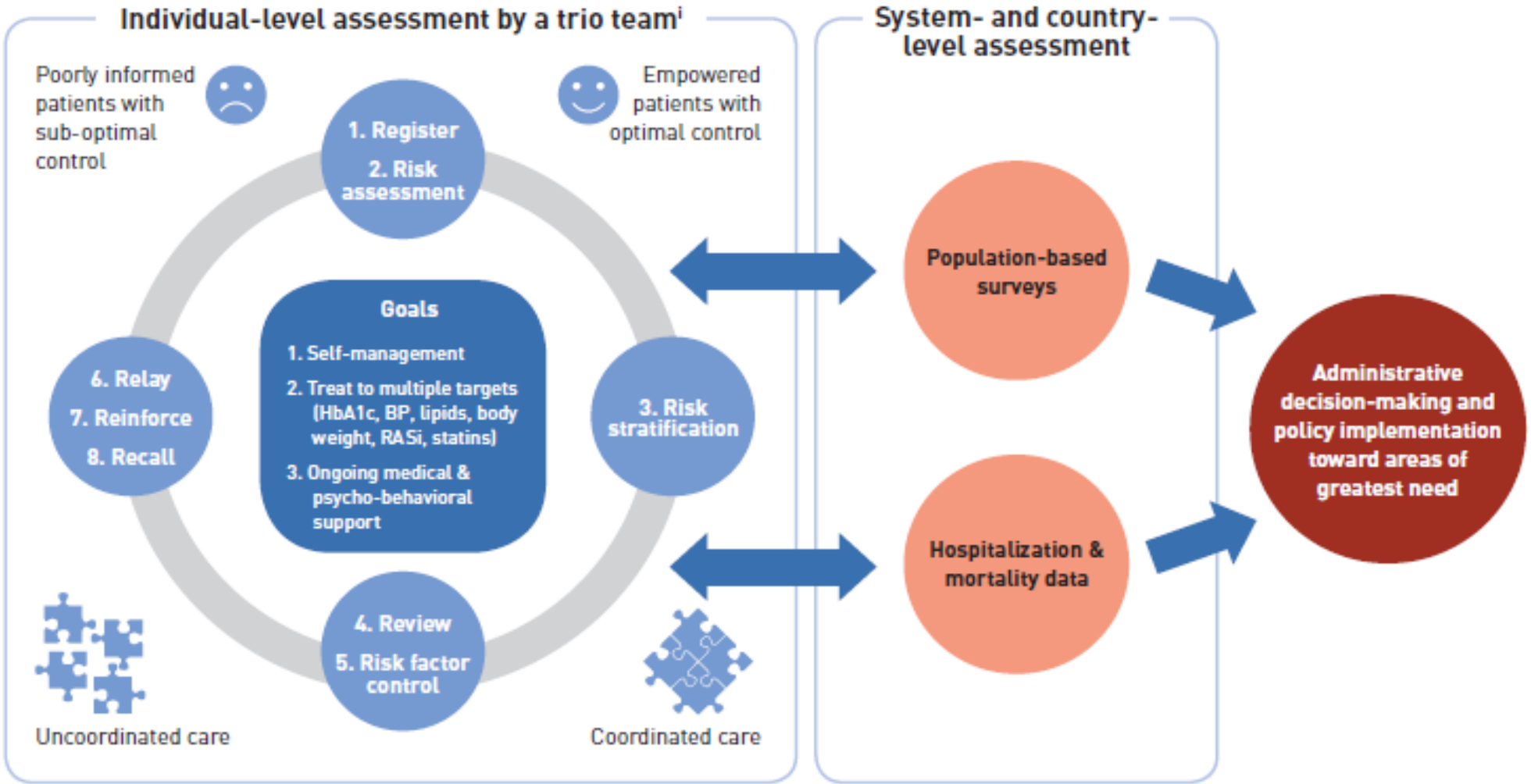


**Figure 12. A schematic diagram showing how fragmented care can transform into data-driven, integrated diabetes care using a trio team including trained nurses and healthcare assistants, supervised by physicians, to collect data systematically during routine clinical practice to establish a register and use the data to empower self-management and treat to multiple targets with ongoing support. The data can be linked to population-based surveys and hospitalisation and mortality date for audit and surveillance purpose to influence policies and practices.**




International Diabetes Federation. IDF Diabetes Atlas, 9th Edition http://www.diabetesatlas.org/ accessed 2nd May 2020

**Figure 13. A schematic diagram showing the combined use of Specialised Diabetes Centres, diabetes teams and diabetes 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.**

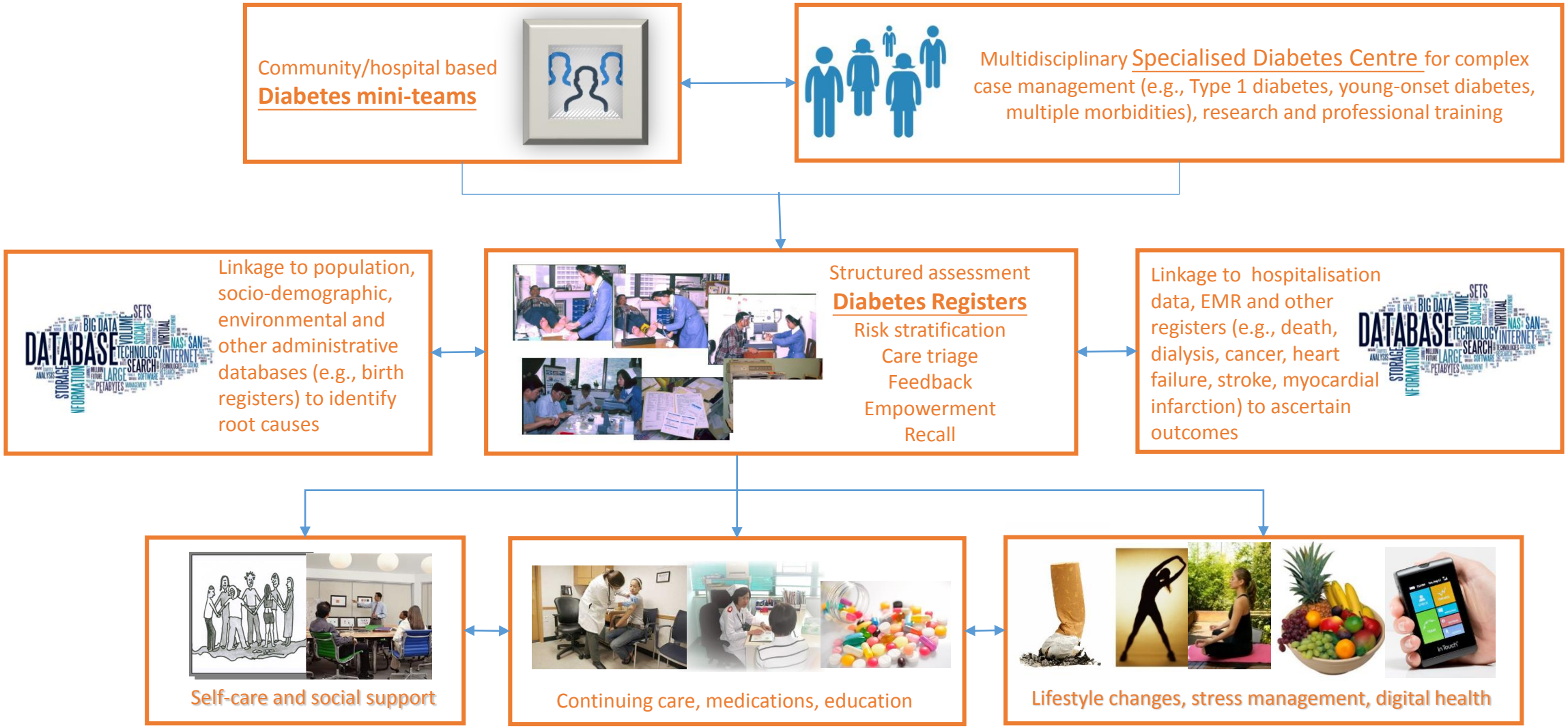
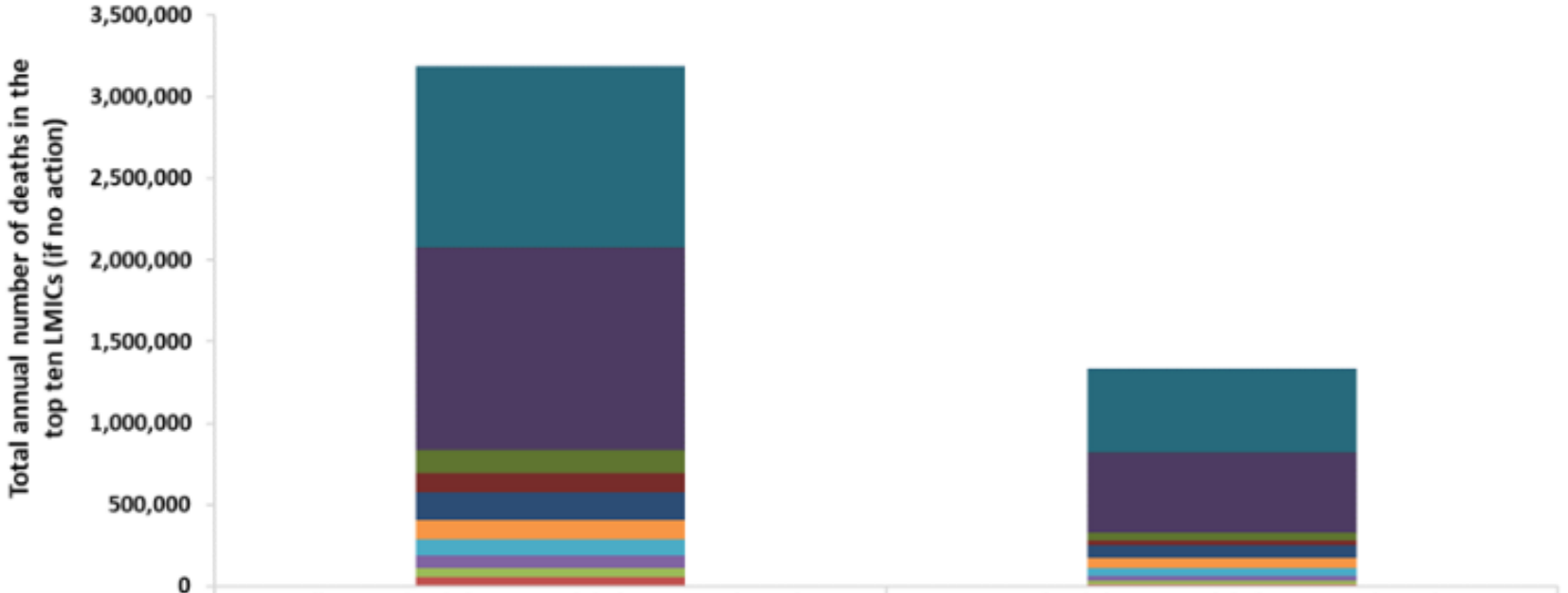
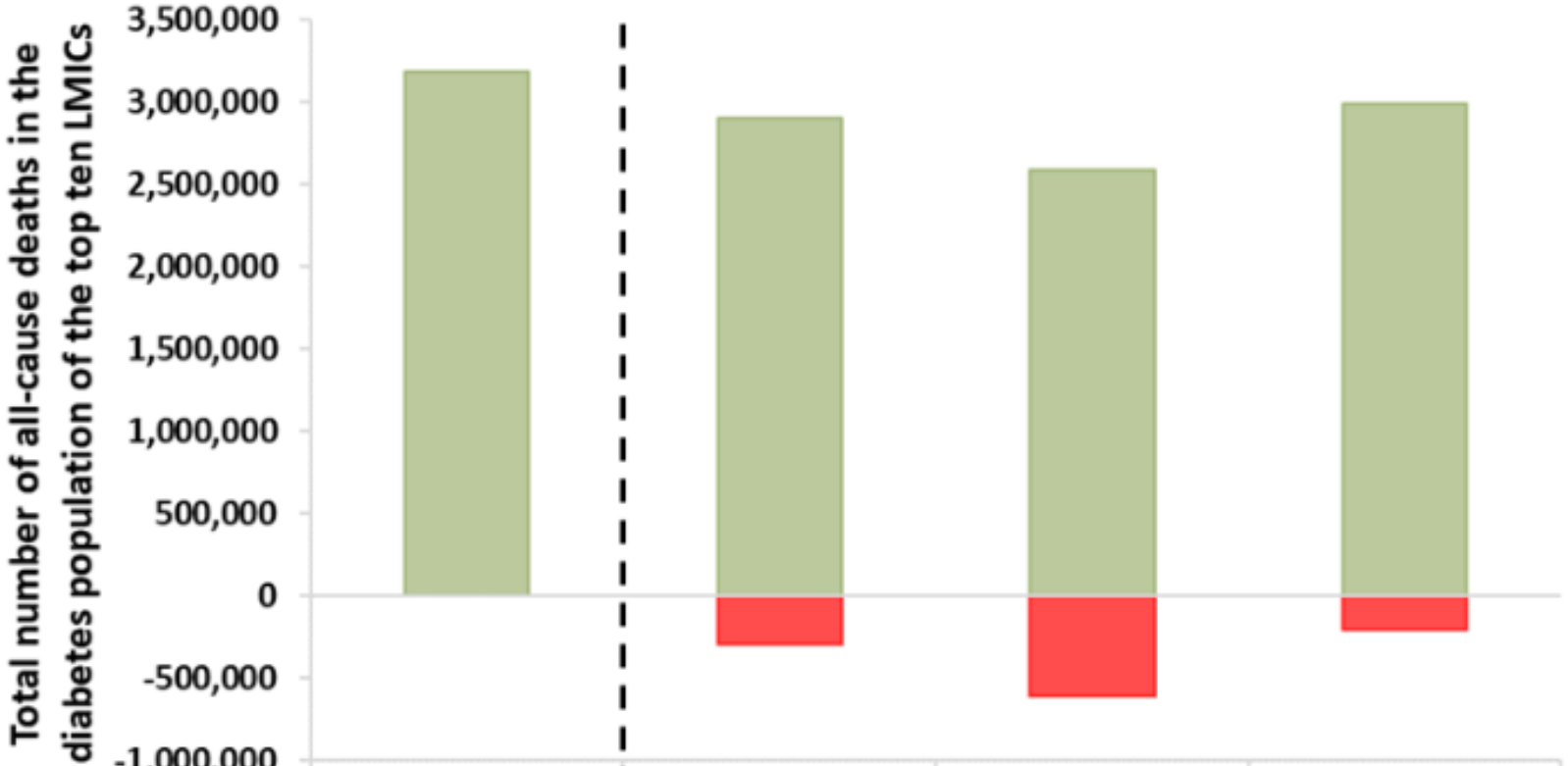


**Figure 14. 3-year estimation of all-cause and CV-death in people with diagnosed diabetes (aged 30-69 years) in the top ten LMICs using WHO and IDF data (2017) and estimated HR of 1.8 (all-cause death) and 2.32 (CV-death) for diabetes based on the Emerging Risk Factors Collaboration.**




| | All-cause death (Diagnosed diabetes population) | CV death (Diagnosed diabetes population) |
|---|---|---|
| China | 1,111,194 | 507,880 |
| India | 1,239,506 | 497,537 |
| Brazil | 140,759 | 46,353 |
| Mexico | 118,833 | 26,055 |
| Indonesia | 173,452 | 80,204 |
| Egypt | 118,609 | 60,875 |
| Pakistan | 99,834 | 49,808 |
| Bangladesh | 74,289 | 31,653 |
| Turkey | 56,205 | 18,585 |
| Thailand | 56,355 | 13,252 |
| Total | 3,189,035 | 1,332,200 |

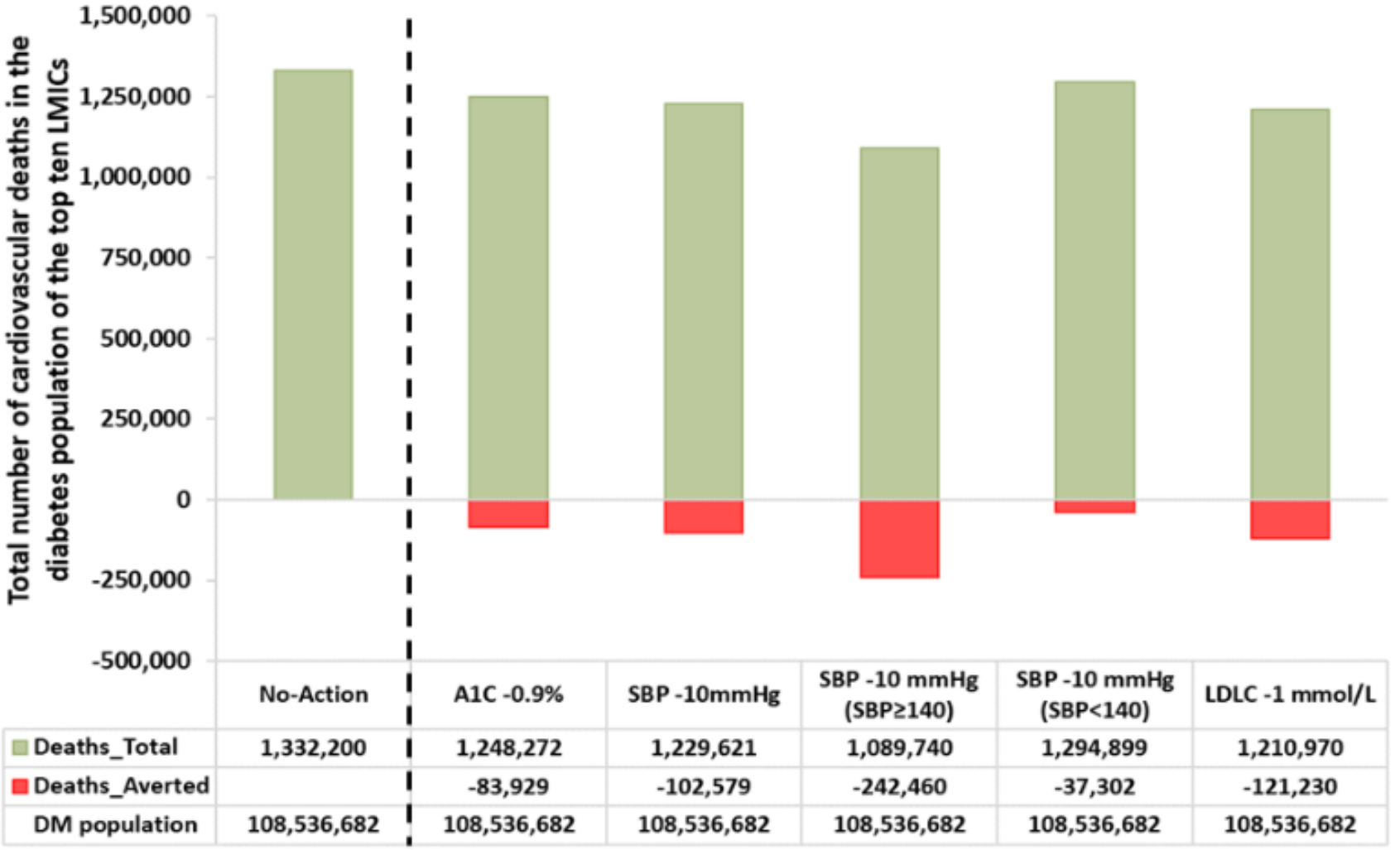
# Fig 15A. 3-year estimation of total number of all-cause deaths with status quo and all-cause deaths averted with interventions in the diagnosed diabetes population aged 30-69 years from the top 10 LMICs




| | No-Action | SBP -10mmHg | SBP -10 mmHg (SBP≥140) | LDLC -1 mmol/L |
|---|---|---|---|---|
| Deaths_Total | 3,189,035 | 2,898,833 | 2,586,307 | 2,988,126 |
| Deaths_Averted | | -290,202 | -602,728 | -200,909 |
| DM population | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) No change in diabetes prevalence and death rate for 3 years; 4) Death rate = birth rate; 5) Sustained effect size for 3 years*

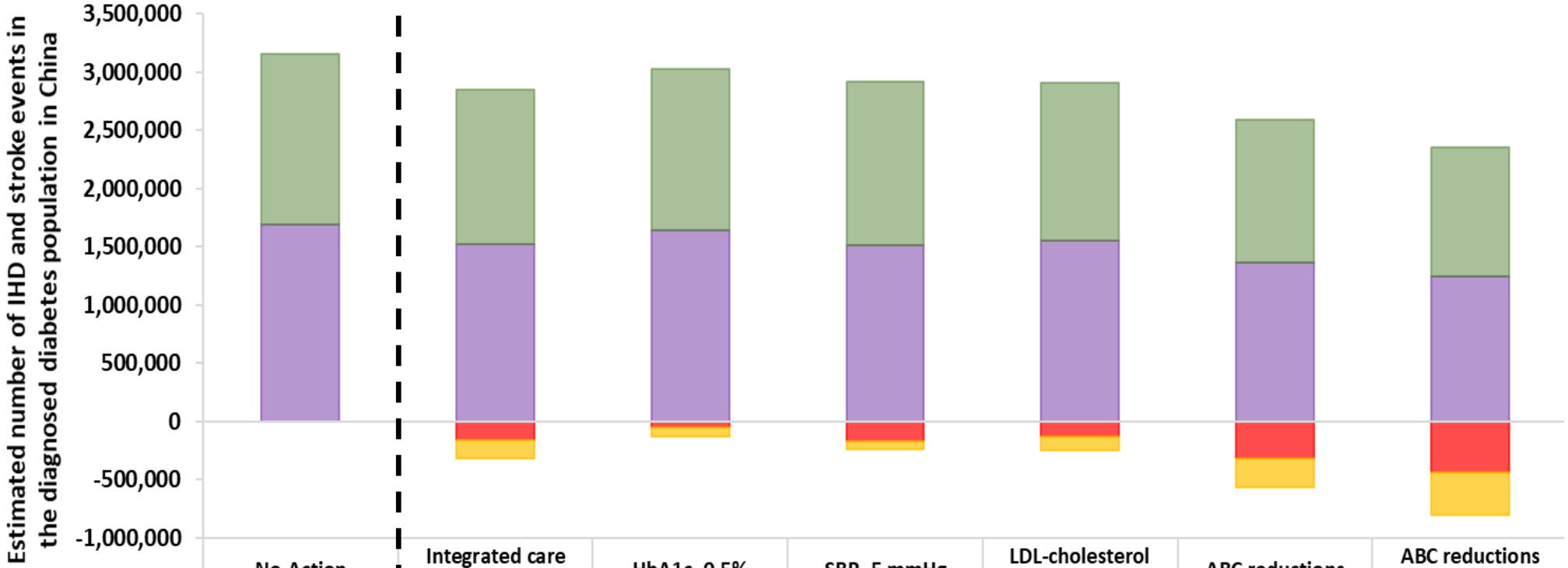
# Fig 15B. 3-year estimation of total number of CV deaths with status quo and CV deaths averted with interventions in diagnosed diabetes population aged 30-69 years from the top 10 LMICs




| | No-Action | A1C -0.9% | SBP -10mmHg | SBP -10 mmHg (SBP≥140) | SBP -10 mmHg (SBP<140) | LDLC -1 mmol/L |
|---|---|---|---|---|---|---|
| Deaths_Total | 1,332,200 | 1,248,272 | 1,229,621 | 1,089,740 | 1,294,899 | 1,210,970 |
| Deaths_Averted | | -83,929 | -102,579 | -242,460 | -37,302 | -121,230 |
| DM population | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 | 108,536,682 |

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) No change in diabetes prevalence and death rate for 3 years; 4) Death rate = birth rate; 5) Sustained effect size for 3 years*

# Fig 16A. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (community-based): Estimated incidence of ischaemic heart disease (IHD )and stroke, and events averted with interventions

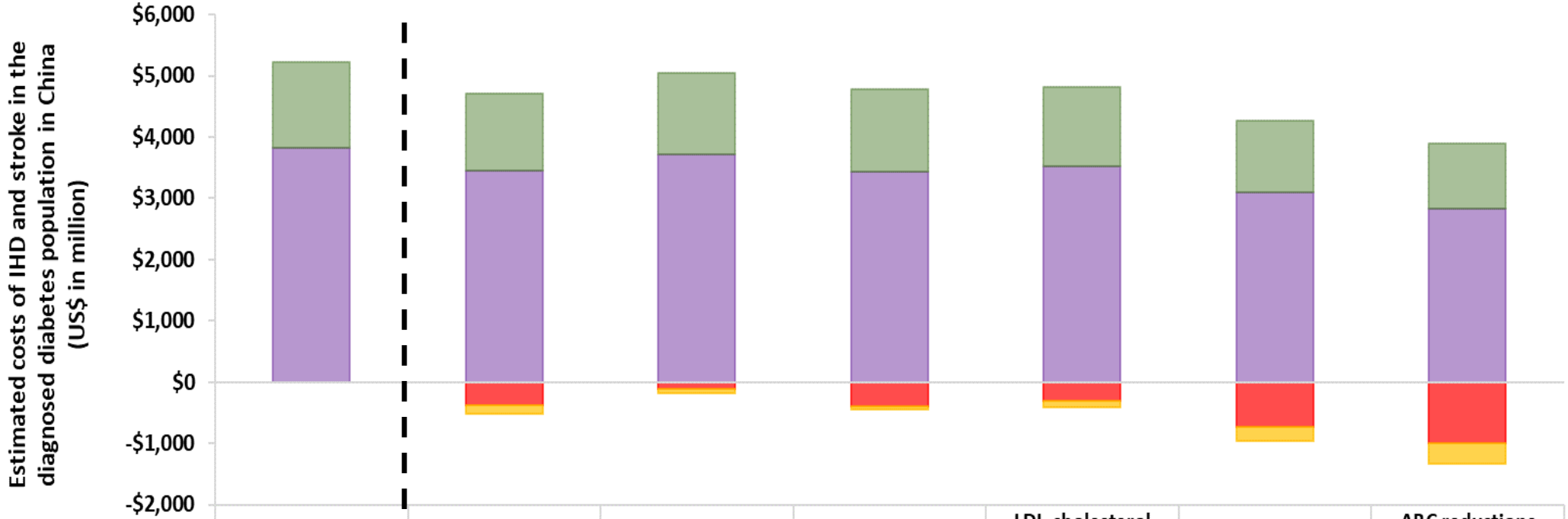



| | No-Action | Integrated care (IC) | HbA1c -0.5% | SBP -5 mmHg | LDL-cholesterol -0.5 mmol/L | ABC reductions | ABC reductions combined with IC |
|---|---|---|---|---|---|---|---|
| IHD_Incidence | 1,470,865 | 1,321,440 | 1,382,673 | 1,407,115 | 1,350,582 | 1,221,214 | 1,108,020 |
| STK_Incidence | 1,686,567 | 1,522,873 | 1,640,356 | 1,514,673 | 1,555,308 | 1,367,432 | 1,247,987 |
| IHD_Averted | | -149,425 | -88,191 | -63,750 | -120,283 | -249,651 | -362,845 |
| STK_Averted | | -163,695 | -46,211 | -171,894 | -131,259 | -319,135 | -438,581 |
| Total_Incidence | 3,157,432 | 2,844,312 | 3,023,030 | 2,921,787 | 2,905,890 | 2,588,645 | 2,356,007 |
| Total_Averted | | -313,120 | -134,402 | -235,644 | -251,542 | -568,786 | -801,425 |
| DM Population | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 |

**China NCD Surveillance cohort:**
$HbA_{1c}$ 7.2%
SBP 144.2 mmHg
LDLC 2.59 mmol/L

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. ABC refers to Hb**A**$_{1C}$, systolic **B**lood pressure and LDL-**C**holesterol.*

# Fig 16B. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (community-based): Estimated costs incurred and saved for ischaemic heart disease (IHD) and stroke with interventions

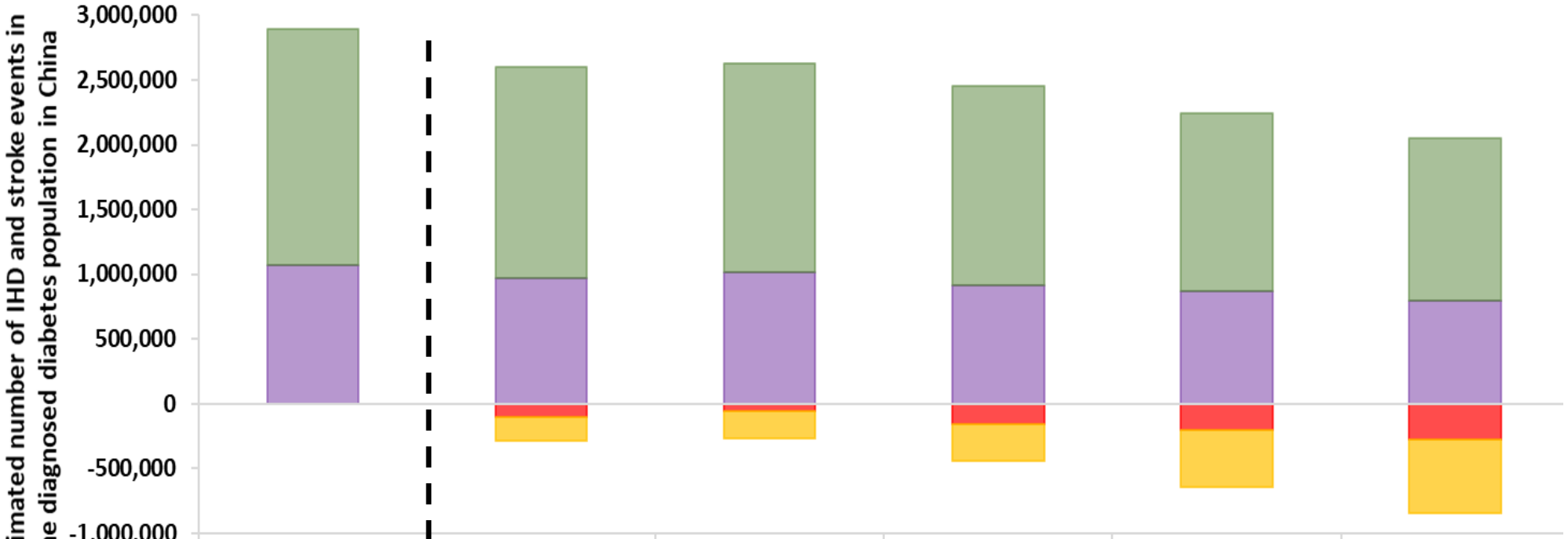



| | No-Action | Integrated care (IC) | HbA1c -0.5% | SBP -5 mmHg | LDL-cholesterol -0.5 mmol/L | ABC reductions | ABC reductions combined with IC |
|---|---|---|---|---|---|---|---|
| IHD_cost incurred | $1,399 | $1,257 | $1,315 | $1,338 | $1,285 | $1,162 | $1,054 |
| Stroke_cost incurred | $3,829 | $3,457 | $3,724 | $3,438 | $3,531 | $3,104 | $2,833 |
| IHD_cost saved | | -$142 | -$84 | -$61 | -$114 | -$237 | -$345 |
| Stroke_cost saved | | -$372 | -$105 | -$390 | -$298 | -$724 | -$996 |
| Total_cost incurred | $5,228 | $4,714 | $5,039 | $4,777 | $4,815 | $4,266 | $3,887 |
| Total_cost saved | - | -$514 | -$189 | -$451 | -$412 | -$962 | -$1,341 |

**China NCD Surveillance cohort:**
$HbA_{1c}$ 7.2%
SBP 144.2 mmHg
LDLC 2.59 mmol/L

a. *The combined public and private direct medical costs per event in China: US$ 951 for CHD, US$ 2,270 for stroke (assumed no baseline complications).*
b. *CKD, ESRD and PVD are excluded in the calculation and thus, these are underestimations. *Integrated care (task shifting).*
c. *Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. ABC refers to Hb**A**$_{1C}$, systolic **B**lood pressure and LDL-**C**holesterol.*

# Fig 17A. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (clinic-based): Estimated incidence of ischaemic heart disease (IHD) and stroke, and events averted with interventions

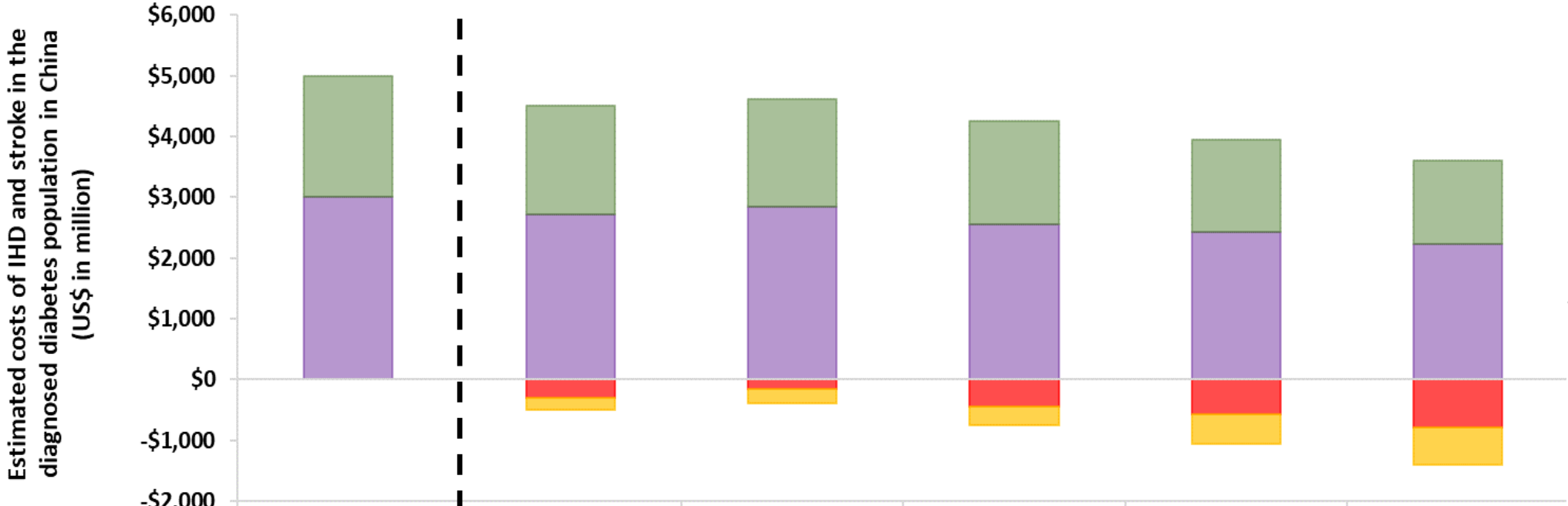



| | No-Action | Integrated care (IC) | HbA1c -1% | LDL-cholesterol -1 mmol/L | AC reductions | AC reductions combined with IC |
|---|---|---|---|---|---|---|
| IHD_Incidence | 1,818,568 | 1,634,014 | 1,610,119 | 1,538,509 | 1,375,918 | 1,255,538 |
| Stroke_Incidence | 1,075,112 | 970,671 | 1,017,148 | 917,071 | 871,279 | 795,126 |
| IHD_Averted | | -184,554 | -208,450 | -280,060 | -442,650 | -563,031 |
| Stroke_Averted | | -104,441 | -57,964 | -158,042 | -203,833 | -279,987 |
| Total_Incidence | 2,893,681 | 2,604,686 | 2,627,267 | 2,455,580 | 2,247,197 | 2,050,663 |
| Total_Averted | | -288,995 | -266,414 | -438,101 | -646,484 | -843,018 |
| DM Population | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 | 57,197,400 |

**China JADE study:**
$HbA_{1c}$ 7.9%
SBP 125.8 mmHg
LDLC 2.94 mmol/L
Disease duration
5 years

*Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. AC refers to Hb**A**$_{1C}$ and LDL-**C**holesterol.*

# Figure 17B. 3-year projection to the diagnosed diabetes population aged 20-79 years in China (clinic-based): Estimated costs incurred and saved for ischaemic heart disease (IHD) and stroke with interventions

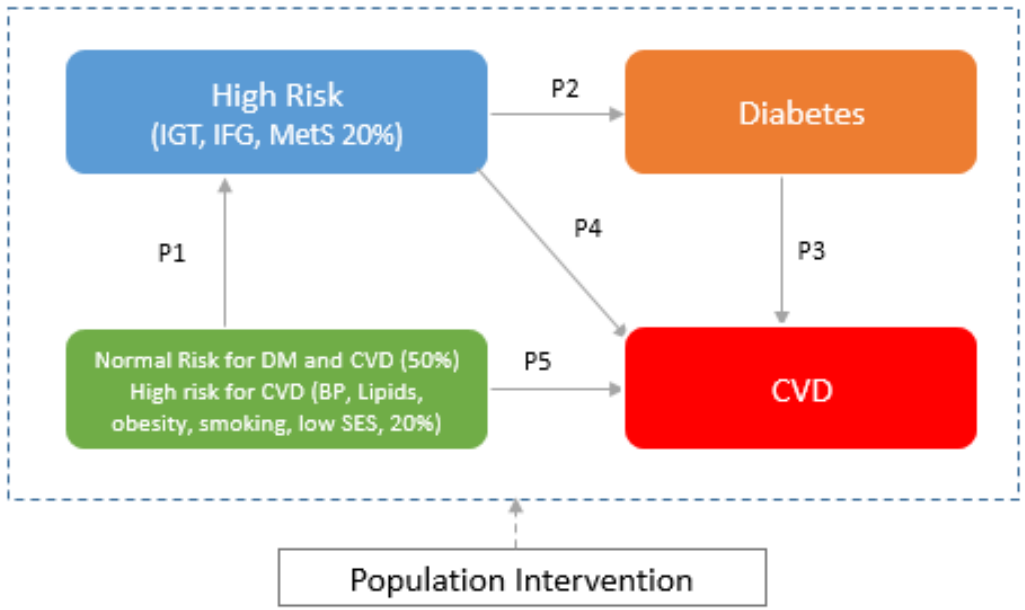



| | No-Action | Integrated care (IC) | HbA1c -1% | LDL-cholesterol -1 mmol/L | AC reductions | AC reductions combined with IC |
|---|---|---|---|---|---|---|
| IHD_cost incurred | $1,999 | $1,796 | $1,770 | $1,691 | $1,512 | $1,380 |
| Stroke_cost incurred | $3,004 | $2,712 | $2,842 | $2,563 | $2,435 | $2,222 |
| IHD_cost saved | | -$203 | -$229 | -$308 | -$487 | -$619 |
| Stroke_cost saved | | -$292 | -$162 | -$442 | -$570 | -$782 |
| Total_cost incurred | $5,003 | $4,509 | $4,612 | $4,254 | $3,947 | $3,602 |
| Total_cost saved | | -$495 | -$391 | -$749 | -$1,056 | -$1,401 |

**China JADE study:**
$HbA_{1c}$ 7.9%
SBP 125.8 mmHg
LDL-C 2.94 mmol/L
Disease duration
5 years

a. *The combined public and private direct medical costs per event in China: US$ 1,099 for CHD, US$ 2,794 for stroke (assumed no baseline complications).*
b. *CKD, ESRD and PVD are excluded in the calculation and thus, these are underestimations. *Integrated care (task shifting).*
c. *Assumptions: 1) 50% diagnosed diabetes population; 2) 70% of diagnosed patients are treated; 3) Diabetes prevalence is maintained for 3 years; 4) Sustained effect size for 3 years. AC refers to Hb**A**$_{1C}$ and LDL-**C**holesterol.*

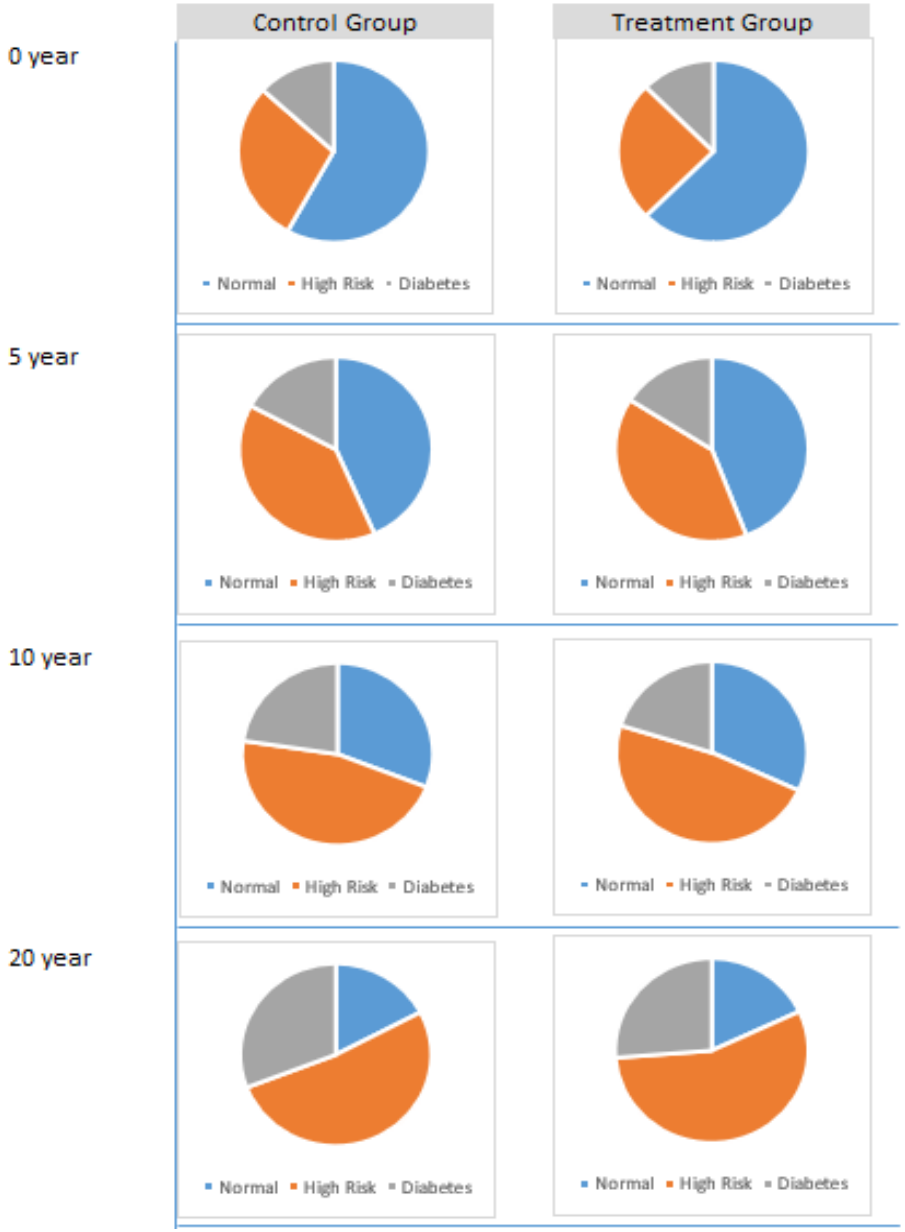
# Figure 18A. Risk factor distribution in 1 million Chinese population and using risk equations to project diabetes/CVD events with or without an integrated society-community-individual strategy aimed at improving health environment, reducing population risk and implementing structured lifestyle modification in high risk individuals




| Table 1. Required information for population distribution | | | |
|---|---|---|---|
| Input Parameters | | | |
| | Age Groups | | |
| Baseline Demographics | <45 | 45~65 | >65 |
| Number of person to intervene | 300,000 | 300,000 | 400000 |
| Proportion of High Risk persons in the intervention population | 10% | 20% | 40% |
| Proportion of Diabetes in the intervention population | 5% | 10% | 20% |
| Proportion of Smokers in the intervention population | 30% | 30% | 30% |
| Annual probability of developing diabetes amongst those at high risk for diabetes | 1.9% | 3.8% | 3.8% |
| Annual probability of moving to high risk amongst those at low risk for diabetes | 5% | 8% | 10% |

| Table 2. Specify the baseline values for diabetes and CVD for the intervention population | | | |
|---|---|---|---|
| Normal Risk | <45 | 45~65 | >65 |
| Average HbA1c | 5.5% | 5.5% | 5.5% |
| Average BMI | 21.6 | 23.3 | 23.1 |
| Average SBP | 110 | 119 | 118 |
| Average Total Cholesterol | 4.23 | 4.56 | 4.53 |
| Average HDL | 1.30 | 1.30 | 1.30 |
| High Risk | | | |
| Average HbA1c | 6.0% | 6.0% | 6.0% |
| Average BMI | 23 | 25 | 25 |
| Average SBP | 119 | 129 | 128 |
| Average Total Cholesterol | 4.63 | 4.99 | 4.95 |
| Average HDL | 1.30 | 1.30 | 1.30 |
| Diabetes | | | |
| Average HbA1c | 8.5% | 8.0% | 7.5% |
| Average BMI | 23 | 25 | 25 |
| Average SBP | 124 | 134 | 133 |
| Average Total Cholesterol | 4.68 | 5.05 | 5.01 |
| Average HDL | 1.24 | 1.24 | 1.24 |

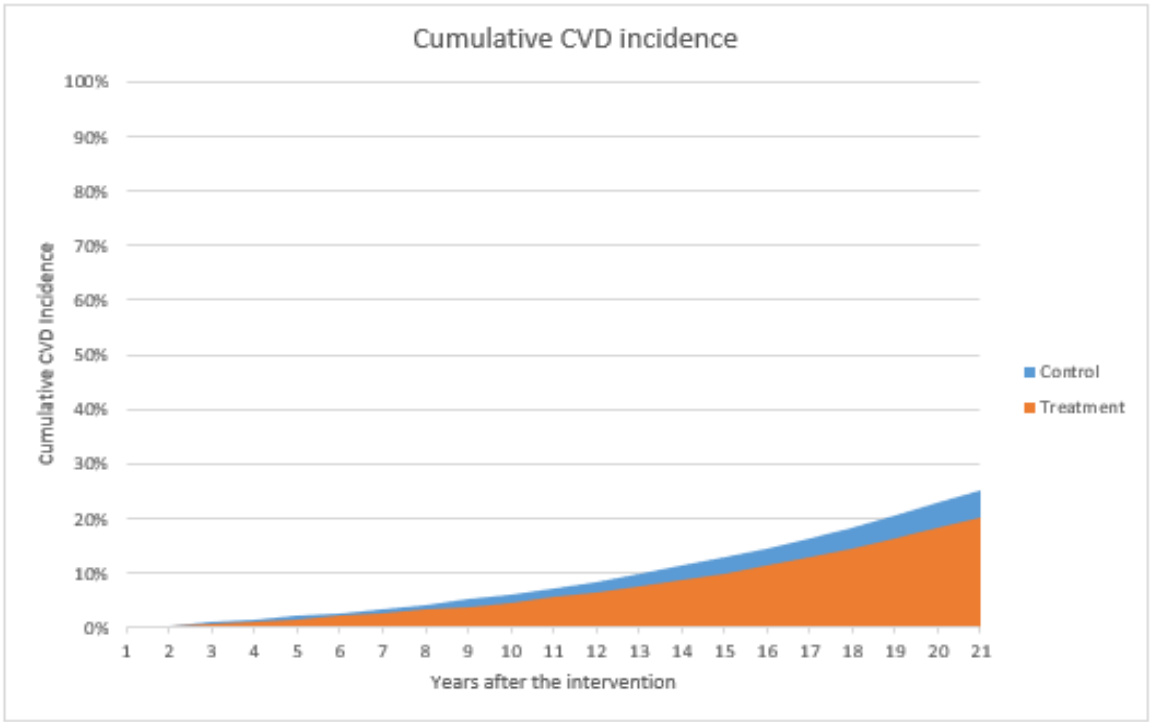
# Figure 18B. 20-year projection of diabetes and CVD events in 1 million people in China with or without an integrated society-community-individual strategy.



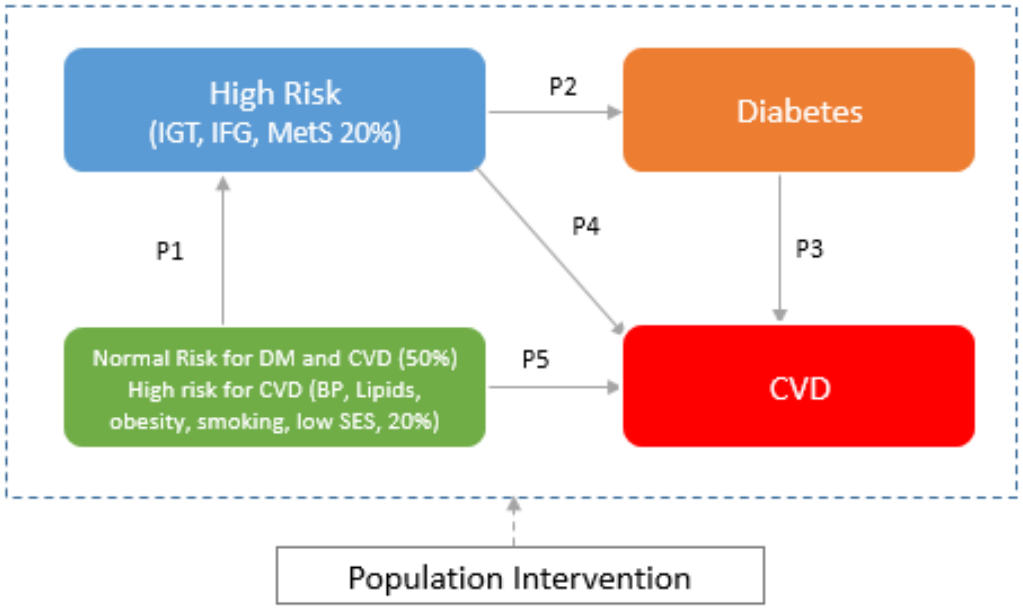

Simulation Results

| Number of Diabetes Prevented * | Events | Relative Risk Reduction |
|---|---|---|
| 5 years | 11065 | 75.33% |
| 10 years | 22489 | 76.24% |
| 20 years | 33773 | 76.43% |
| **Number of CVD Prevented *** | **Events** | **Relative Risk Reduction** |
| 5 years | 6617 | 75.37% |
| 10 years | 17270 | 76.14% |
| 20 years | 51863 | 79.53% |

* (Control-Intervention)



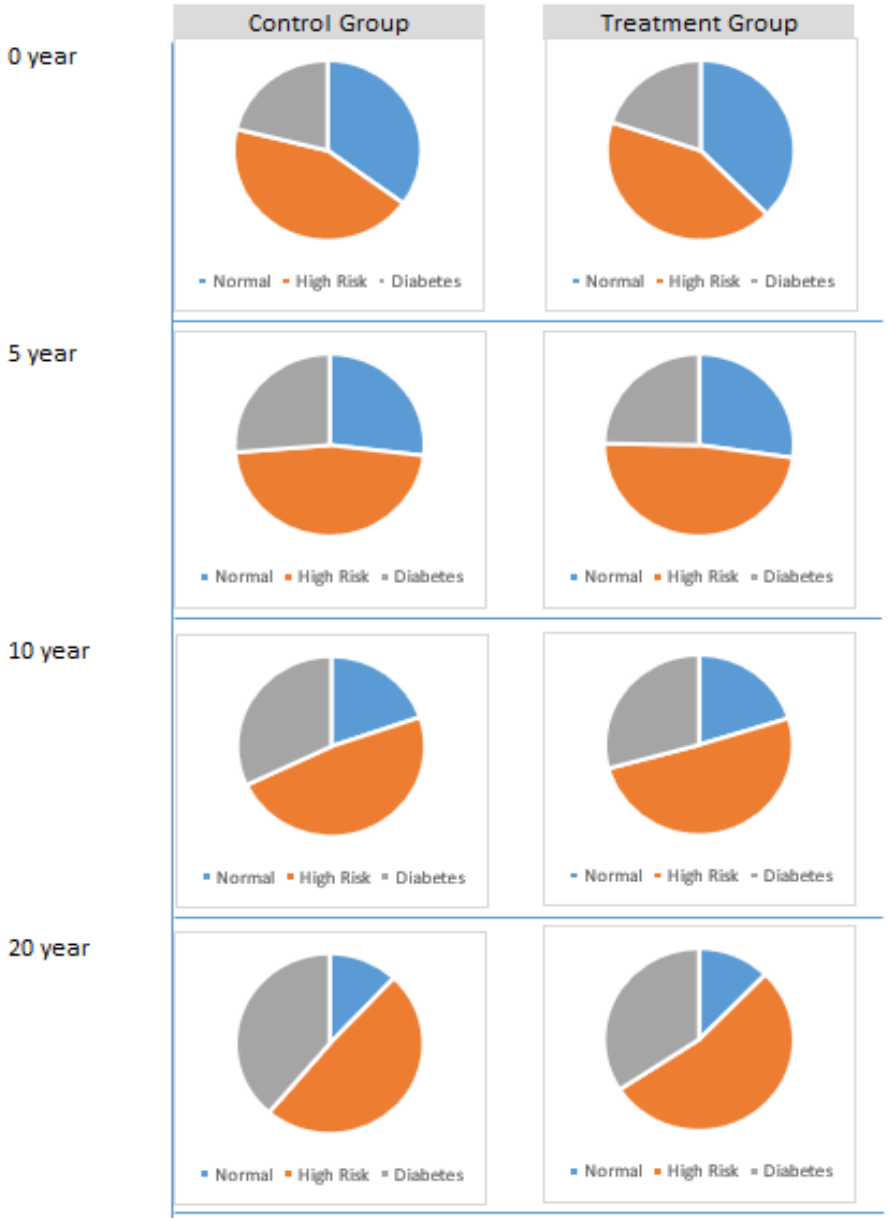
# Figure 19A. Risk factor distribution in 1 million Brazilian population and using risk equations to project diabetes/CVD events with or without an integrated society-community-individual strategy aimed at improving health environment, reducing population risk and implementing structured lifestyle modification program in high risk individuals




| Table 1. Required information for population distribution | | | |
|---|---|---|---|
| Input Parameters | | | |
| | Age Groups | | |
| Baseline Demographics | <45 | 45~65 | >65 |
| Number of person to intervene | 300,000 | 300,000 | 400000 |
| Proportion of high risk persons in the intervention population | 34% | 44% | 48% |
| Proportion of diabetes in the intervention population | 6% | 19% | 31% |
| Proportion of smokers in the intervention population | 10% | 14% | 9% |
| Annual probability of developing diabetes amongst those at high risk for diabetes | 1.9% | 3.8% | 3.8% |
| Annual probability of moving to high risk amongst those at low risk for diabetes | 5% | 8% | 10% |

| Table 2. Specify the baseline values for diabetes and CVD for the intervention population | | | |
|---|---|---|---|
| Normal Risk | <45 | 45~65 | >65 |
| Average HbA1c | 5.07% | 5.18% | 5.31% |
| Average BMI | 25 | 25 | 25 |
| Average SBP | 112 | 117 | 127 |
| Average Total Cholesterol | 5.19 | 5.63 | 5.63 |
| Average HDL-C | 1.5 | 1.6 | 1.7 |
| High Risk | | | |
| Average HbA1c | 5.18% | 5.30% | 5.38% |
| Average BMI | 27 | 28 | 27 |
| Average SBP | 118 | 123 | 131 |
| Average Total Cholesterol | 5.41 | 5.72 | 5.56 |
| Average HDL-C | 1.4 | 1.4 | 1.5 |
| Diabetes | | | |
| Average HbA1c | 6.50% | 6.70% | 6.60% |
| Average BMI | 31 | 29 | 28 |
| Average SBP | 122 | 129 | 135 |
| Average Total Cholesterol | 5.43 | 5.62 | 5.27 |
| Average HDL-C | 1.29 | 1.37 | 1.38 |

# Figure 19B. 20-year projection of diabetes and CVD events in 1 million people in Brazil with or without an integrated society-community-individual strategy.




Simulation Results

| Number of Diabetes Prevented * | Events | Relative Risk Reduction |
|---|---|---|
| 5 years | 14407 | 76.01% |
| 10 years | 24564 | 77.38% |
| 20 years | 27997 | 77.83% |
| **Number of CVD Prevented *** | **Events** | **Relative Risk Reduction** |
| 5 years | 6855 | 75.38% |
| 10 years | 17892 | 76.18% |
| 20 years | 52991 | 79.78% |

* (Control-Intervention)

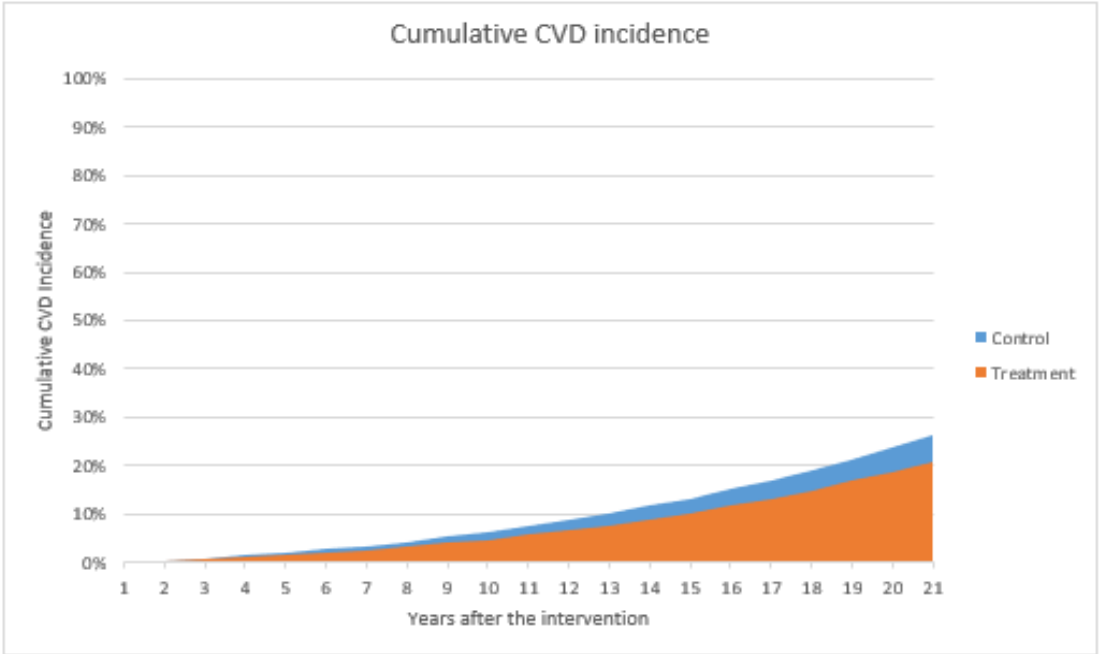


**Figure 20. A systematic review showing the trends of annual incidence of diabetes during 1992-2014 among people aged 55-69. Most of the declining trends occur in high-income countries (HICs) with paucity of information in low- and middle-income countries. These data highlight the importance of societal determinants where key upstream factors notably, better education system, good governance and social policies in HICs may underline these favorable trends, calling for both population and individual-based strategies for prevention and control of diabetes and NCD (Magliano DJ et al, BMJ 2019).**