Diabetes: a 21st century challenge

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Lancet Diabetes Endocrinol 2014; 2: 56–64

Published Online December 4, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70112-8

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The number of people with diabetes worldwide has more than doubled during the past 20 years. One of the most worrying features of this rapid increase is the emergence of type 2 diabetes in children, adolescents, and young adults. Although the role of traditional risk factors for type 2 diabetes (eg, genetic, lifestyle, and behavioural risk factors) has been given attention, recent research has focused on identifying the contributions of epigenetic mechanisms and the effect of the intrauterine environment. Epidemiological data predict an inexorable and unsustainable increase in global health expenditure attributable to diabetes, so disease prevention should be given high priority. An integrated approach is needed to prevent type 2 diabetes, taking into account its many origins and heterogeneity. Thus, research needs to be directed at improved understanding of the potential role of determinants such as the maternal environment and other early life factors, as well as changing trends in global demography, to help shape disease prevention programmes.

Introduction

Lifestyle changes and globalisation have, during the past five decades, resulted in remarkable changes in societies, political systems, the environment, and human behaviour. The number of people with diabetes and obesity has increased substantially in both developed and developing countries,[1,2] with the greatest burden tending to fall on socially disadvantaged groups and Indigenous peoples. Diabetes ranks highly on the international health agenda as a global pandemic and as a threat to human health and global economies,[2] and has been termed "the diabetes apocalypse" by Edwin Gale (Gale E, University of Bristol, personal communication).

In 1971, when Bennett and colleagues[3] reported the very high prevalence of diabetes in the American Pima Indians (50% for adults older than 35 years), who could have predicted that this was the harbinger of a worldwide diabetes epidemic? Yet, diabetes (predominantly type 2 diabetes), long thought of as a Cinderella disease, has become a major health challenge of the 21st century, together with other non-communicable diseases such as cardiovascular disease.[4]

After Bennett and colleagues' report,[3] other similar data started to emerge. In 1975, it was reported[5] that the central Pacific island of Nauru had a national diabetes prevalence of more than 34% in people aged 15 years or older—the highest national prevalence of any country, both at that time and at present. This Micronesian population had become almost totally westernised,[6] or, as Arthur Koestler[7] aptly described, had undergone "Coca-colonisation". In the case of Nauru, the profound and rapid lifestyle changes were caused by wealth from mining of rich phosphate deposits on the island. Findings from further studies in the Pacific islands[8–12] confirmed the high prevalence of diabetes in this region. Furthermore, accumulated evidence from the past 20–30 years shows a rapidly increasing burden of diabetes worldwide.[1,2] Paradoxically, the burden of this so-called western disease, caused by western lifestyles, has the greatest effect on developing countries; more than 80% of the global total of people with diabetes live in these countries.

Recognition of the challenge of diabetes

International health agencies and national governments ignored the rise and rise of diabetes and other non-communicable diseases until quite recently. Funding for the prevention and control of such diseases (including diabetes) was of low priority compared with funding for the control of communicable diseases.[13] Against this background, in 2006 the UN General Assembly unanimously passed Resolution 61/225,[14] calling for diabetes to be recognised as an international public health challenge. In 2011, the UN General Assembly made a political declaration on the prevention and control of non-communicable diseases,[15] which was followed by a call by the World Health Assembly to reduce avoidable mortality from non-communicable diseases by 25% by 2025.[16] Since this World Health Assembly initiative, major concerns have arisen as to whether governments are genuinely committed to this goal and whether the target will be met. As Richard Horton,[17] Editor of *The Lancet*, wrote, it remains true that, despite global rhetoric and resolutions, non-communicable diseases are still the least recognised group of conditions that threaten the future of human health and wellbeing.

The diabetes epidemic and its consequences result from the interaction of intricate genetic and epigenetic systems within a complex societal structure that includes many behavioural and environmental effects. In this Review, we address some of the key challenges that the diabetes epidemic, predominantly of type 2 diabetes, presents to society in the 21st century. These challenges include large increases in the prevalence of type 2 diabetes and the increasing burden of the disease in young people, including children. We also note the importance of the intrauterine environment and epigenetic factors, and the economic cost of the diabetes epidemic to individuals and nations.

Global predictions and patterns

Since 1994, when the first global predictions of a major increase in the number of people with diabetes were published,[18] many efforts have been made by both the

International Diabetes Federation and WHO[19] to regularly update these figures. In 1994, 110 million people worldwide were estimated to have diabetes, and by 2010 the number was predicted to increase to 239 million.[18] In 1998, King and colleagues[19] reported that 135 million people had diabetes in 1995, and predicted that 300 million would have the disease by 2025. A later report suggested that 171 million people had diabetes in 2000, which would increase to 366 million by 2030.[20] However, recent findings suggest that the burden was consistently underestimated.[21] The latest prediction from the International Diabetes Federation is that 382 million people are living with diabetes in 2013 (a number previously forecast for 2030), and that by 2035 the number will be almost 600 million.[22] Figure 1 shows the global distribution of people with types 1 and 2 diabetes by International Diabetes Federation regions; the Western Pacific region has by far the highest number.

The International Diabetes Federation Diabetes Atlas provides predictions for the ten countries with the largest diabetes populations (table).[22] Of these countries, four are in Asia (China, India, Indonesia, and Japan). Asia is the centre of the global epidemic of diabetes, as a result of rapid economic development, urbanisation, and nutritional transition.[23] The Gulf region in the Middle East is another area where these factors are causing substantial increases in the number of people with diabetes.[24] The major burden of diabetes is now in developing rather than developed countries; about 80% of people with diabetes live in low-income and middle-income countries and communities.[25] This distribution presents yet another important challenge for the future, because most people with diabetes live in countries with inadequate resources for treatment. The increased risks of premature morbidity and mortality will have major social and economic consequences for these countries and communities. In developed countries, the prevalence of diabetes is typically higher for immigrants from less developed regions than for the host population.[26,27] Furthermore, even higher prevalences of diabetes occur in Indigenous peoples in developed nations (eg, in Australia[28] and Canada[29]).

Diabetes in developing countries presents several challenges that differ from those in developed countries. First, the rapid growth in diabetes in developing countries is in adults younger than 60 years, rather than in elderly people. Disease in this younger age group thus affects working people and carers. Second, the range of complications in the main ethnic groups living in most developing countries often includes more kidney disease and stroke, and less coronary artery disease, than in white populations of European origin. Third, in developing countries, attitudes towards diabetes amongst families, friends, and coworkers can make acceptance and self-management more difficult for people with diabetes.[30] Fourth, health-care systems in developing countries are much more geared towards treatment of acute, symptomatic presentations of single diseases, rather than management of many overlapping and asymptomatic chronic conditions. Finally, research into therapeutics

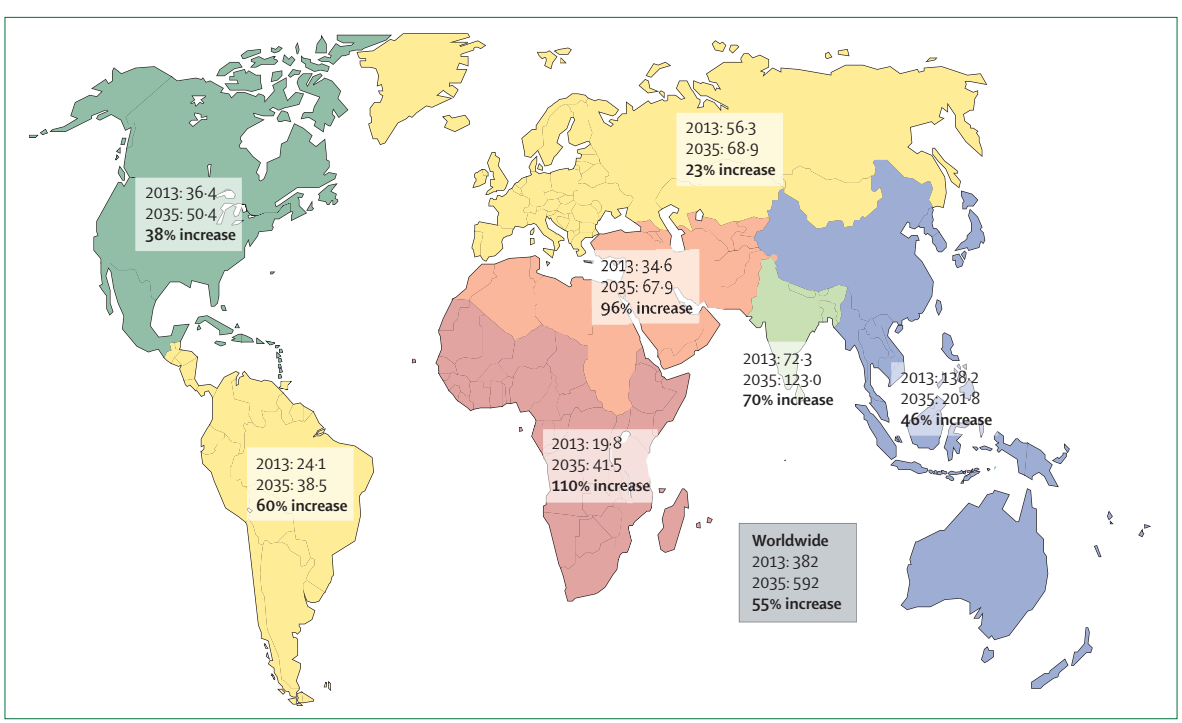

Figure 1: **Number of people estimated to have diabetes (millions)**
Data adapted from the International Diabetes Federation Diabetes Atlas, 6th edition.[21]

	Country ranking 2013	Number of people with diabetes (millions), 2013	Country ranking 2035	Number of people with diabetes (millions), 2035
1	China	98·4	China	142·7
2	India	65·1	India	109·0
3	USA	24·4	USA	29·7
4	Brazil	11·9	Brazil	19·2
5	Russia	10·9	Mexico	15·7
6	Indonesia	8·6	Indonesia	14·2
7	Mexico	8·4	Egypt	13·1
8	Egypt	7·5	Pakistan	12·8
9	Japan	7·2	Turkey	11·8
10	Turkey	7·0	Russia	11·2

Source: International Diabetes Federation Diabetes Atlas.[22]

Table: **Countries with the highest numbers of people with diabetes**

focuses on expensive new drugs, which are unaffordable for millions of people, with little funding for strategies for improvement in resource-limited settings.

Secular trends in the type 2 diabetes epidemic

Evidence of increasing prevalence

The study of the occurrence of diabetes over long periods (ie, secular trends) shows the magnitude and speed of the evolution of this epidemic. Although the situation in Nauru was an early warning of the global epidemic, studies in the Indian-Ocean island of Mauritius provide another indicator of the seriousness of the global epidemic.[8,31]

Mauritius has a population of 1·3 million, predominantly of Asian-Indian (68%), African (27%), and Chinese (3%) ethnicity. The study in Mauritius covered a 23 year period, and its findings showed a notable significant increase in the prevalence of diabetes from 12·8% in 1987, to 17·9% in 1998, and to 23·4% in 2009.[31] The ethnic distribution in Mauritius is similar to that of almost two-thirds of the global population. On this basis, in 1987, with modernisation and globalisation, diabetes rates in China and India were predicted to increase substantially.[8]

Findings from studies from China and India support this prediction.[22] The prevalence of diabetes in Shanghai, China, which was very low in 1980,[32] had increased ten-fold in some areas within two decades.[33,34] The prevalence of diabetes in Qingdao also increased substantially between 2001–02 and 2006,[35] from 11·3% for both men and women in 2001–02, to 19·2% for men and 16·1% for women in 2006. Similar increases in prevalence were also reported in rural areas.[35] Findings from a national 2007–08 survey suggest that China now has more people with diabetes than has any other nation in the world, with 92 million people affected—almost one in ten adults.[23] In India, findings from a 2008 report showed a marked increase in diabetes prevalence in both urban areas (from 13·9% in 2000 to 18·2% in 2006) and rural areas (from 6·4% in 2000 to 9·2% in 2006).[36] Other studies have also shown increases in diabetes prevalence over time in India.[37] Yet another example of a substantial secular increase in diabetes prevalence comes from Turkey.[38] Findings from a cross-sectional national study in 1997–98 showed a prevalence of 7·2% in people aged 20 years and older. In 2010, a repeat national study showed an age-standardised prevalence of 13·7%, a 90% increase in a 12 year period.[24] Even in predominantly white populations of European origin, secular increases have been noted. For example, diabetes prevalence in Ontario, Canada, increased by 69% (from 5·2% to 8·8%) between 1995 and 2005.[39]

Although the highest prevalence of diabetes has been reported in large urban centres, particularly in India, the most pronounced increases in prevalence have been in rural populations. A systematic review[40] of diabetes prevalence in rural populations of low-income and middle-income countries found that the prevalence of diabetes in 2005–10 was nearly five times higher (8·6%) than that reported in 1985–89 (1·8%).

The global increase in urbanisation and technology has been associated with decreasing physical activity, which might exacerbate the epidemic of type 2 diabetes. Ng and Popkin[41] reported substantial reductions in physical activity and increased sedentary behaviour in a study that used cross-sectional and longitudinal datasets from five countries (Brazil, China, India, the UK, and the USA). The authors noted that reduced activity and increased sedentary behaviour worldwide will represent a major threat to health, as a result of the potential effect on weight gain and other cardiometabolic health risks.

Evidence of decreasing prevalence

During World War 2, the incidence of diabetes decreased in the civilian populations of occupied territories.[42] Is there any recent evidence to suggest a secular decrease in diabetes in any nation?

In 1975, Nauru had a high prevalence of diabetes.[5] The country became independent in 1968, and the income from its rich phosphate deposits made the Nauruans extremely wealthy,[6] which led to major lifestyle changes. Imported food was plentiful, the Nauruans led sedentary lives, and the prevalence of type 2 diabetes increased substantially.[5] In the past decade, with exhaustion of the phosphate deposits, the national economy has contracted sharply and imported foods have become less readily available. A 2004 survey of diabetes in people aged 15–64 years in Nauru showed a pronounced downward trend over three decades: the reported diabetes prevalence, based on fasting plasma glucose concentrations, was 13·7% in 2004,[43] compared with 24.4% in 1975.[44] This decrease could be a result of the dramatic downturn in the Nauru economy over this period, because no organised prevention activities had been implemented. These findings emphasise the important role that socioeconomic factors could have in

incidence, prevalence, and mortality patterns for type 2 diabetes and cardiovascular disease, as has been shown to be the case in Cuba.[45]

Emergence of type 2 diabetes and prediabetes in youth

The global epidemiology of diabetes is changing. Type 2 diabetes was traditionally thought of as a disorder of middle-aged and elderly people, and almost exclusively as an adult disorder. However, diabetes has become more common, not only in young adults, but also in adolescents and children.[2] This change has occurred predominantly in Indigenous populations and other high-prevalence groups.[2] Earlier age of onset of type 2 diabetes will affect the future global burden of diabetes and prevention activities. It also has important implications for the classification of diabetes in childhood and adolescents. Children and adolescents who are overweight or obese are also presenting with type 1 diabetes with accompanying insulin resistance.[46]

The highest prevalence of type 2 diabetes in children and adolescents occurs in high-risk ethnic groups, which include Indigenous populations (particularly in North America and Australia), Pacific Islanders, African Americans, Hispanics, and some Asian populations.[2,47] The incidence of type 2 diabetes is six times higher in Australian Indigenous youth than in Australian young people generally.[48] Australia's Indigenous people experience a disproportionately high rate of type 2 diabetes, and the most striking feature of the diabetes epidemic in Australia is the premature age of onset.[28,48,49] In New Zealand, the incidence of type 2 diabetes in childhood or adolescence increased by five-fold between 1995 and 2007.[50] Most patients were of Pacific island or Māori ethnicity. In the SEARCH for Diabetes in Youth Study[51] in the USA, young people aged 15–19 years from ethnic-minority populations had a higher incidence of diabetes than did non-Hispanic whites.[51] Between 1995 and 2007, the annual incidence of type 2 diabetes in children younger than 15 years increased five-fold.[51] As obesity in young people increases in Asian countries such as China and India, without effective intervention strategies to reduce obesity, more people will develop type 2 diabetes at younger ages.[52] Yan and colleagues[53] noted, with concern, that the prevalence of diabetes is already higher in Chinese children than in US children.

Management of type 2 diabetes in a child or adolescent is entirely different from that of diabetes in adults.[48] Lifestyle change and adherence to medication are difficult to achieve in this age group, and diabetes onset so early in life usually means many years of disease and treatment. In addition to the effect of long duration of diabetes, other factors (such as poor metabolic control) seem to put adolescents with type 2 diabetes at a particularly high risk of development of both microvascular and macrovascular complications.[54] Indeed, investigators of a recent modelling study estimated that type 2 diabetes that develops between the ages of 15 and 24 years will result in a lifetime risk of microalbuminuria of close to 100%, a lifetime risk of blindness of 20%, and 15 years of life lost.[22] Furthermore, therapeutic options during childhood are limited by the lack of safety and efficacy data for treatments other than insulin in this age group.[55]

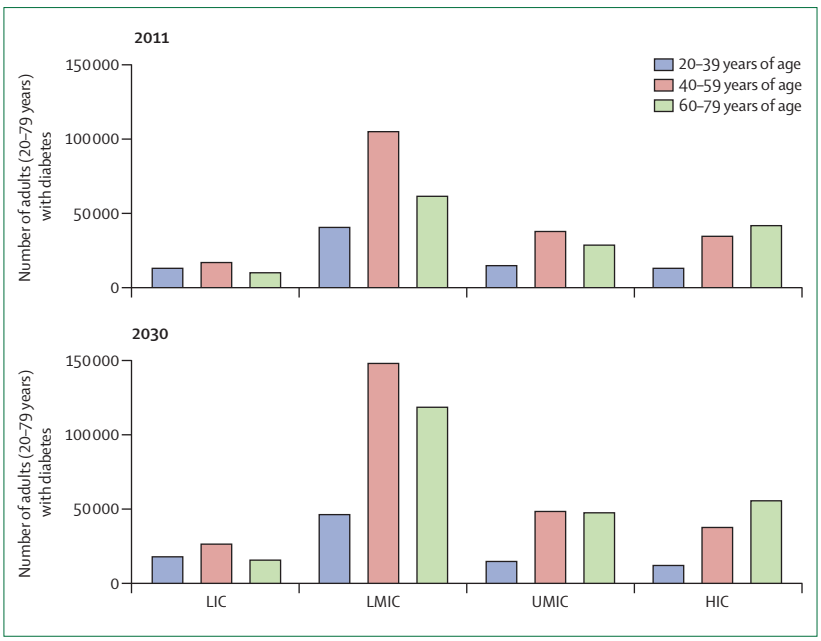

Figure 2: **Numbers of adults estimated to have diabetes by World Bank income group in 2011 and 2030, according to age[21]**
LIC=low-income countries. LMIC: lower-middle-income countries. UMIC=upper-middle-income countries. HIC=high-income countries.

The costs of care in young adults and the lifetime economic effects on productivity associated with diabetes are future challenges, particularly in developing countries. The magnitude of the probable effect of younger onset of disease is obvious in comparisons of age profiles between high-income and low-income countries (figure 2).[21] In low-income and middle-income countries, the largest groups of people with diabetes are of working age (40–59 years). This finding differs from the classic age distribution of diabetes in high-income countries, in which most people with diabetes are aged 60–79 years.

Epigenetics and the developmental origins of type 2 diabetes

The importance of genetic contributions and their interaction with the environment as key risk determinants of type 2 diabetes has long been accepted.[56] In the past 5 years, about 600 genome-wide association studies have examined more than 100 human diseases, uncovering more than 800 genetic variants associated with one or more diseases.[57] However, in nearly every case, most of the factors that cause the disease are still unknown, which has led to growing interest in exploration of non-genetic

factors that could affect disease causation. However, only lately (perhaps in the past decade) have epigenetic pathways and early life events received substantial attention in relation to type 2 diabetes.[58]

The Dutch Hunger Winter famine,[59] which occurred during the late stages of World War 2, provides the basis for a new perspective on the aetiology of type 2 diabetes and other chronic disorders such as hypertension and obesity. In the winter of 1944–45, the German authorities blocked all food supplies to the west of the Netherlands, which was still under occupation. Official rations fell to as low as 500 kcal/day, and widespread starvation ensued.[59] This event provided a natural experiment, because the famine affected infant size at birth, development of the central nervous system, and maternal blood pressure.[59] The mean birthweight of babies who were exposed to the famine during the third trimester of pregnancy was 300 g lower than that of unexposed babies.[59]

Findings from the Dutch famine birth cohort study[60] showed an association between fetal malnutrition and increased diabetes risk in adulthood. Those who had been exposed to famine in utero had worse glucose tolerance in adulthood than those who were not exposed.[60] In other famine situations, such as the 1959–61 Chinese famine,[61] similar findings have been reported. Low birthweight has been consistently associated with an increased risk of development of type 2 diabetes in adult life. In a meta-analysis[62] that included 28 populations, a 1 kg increase in birthweight was associated with a 20% risk reduction in type 2 diabetes.

Nutritional deprivation in utero, and other adverse events such as maternal hyperglycaemia, can affect later susceptibility to obesity, diabetes, other metabolic abnormalities, and cardiovascular disease.[63] Findings from epidemiological and clinical studies in human beings, and experimental studies in animals, have shown that adverse intrauterine events can affect fetal development.[58] An important mechanism for this involves epigenetic modification,[64] which has been defined as heritable changes in gene expression that are not associated with changes in DNA sequence, but rather through DNA methylation and histone modification. Six decades after the famine, individuals exposed in utero to the Dutch Hunger Winter had less DNA methylation of the imprinted *IGF2* gene than did their unexposed same-sex siblings. This association was specific for periconceptional exposure.[65] So, why are epigenetic changes important to public health? Epigenetic changes can be transmitted through future generations.[58]

The risk of type 2 diabetes as a result of inadequate fetal nutrition is probably exacerbated in people who are exposed to more affluent nutritional environments in adult life, and who have excess and rapid weight gain in early adulthood. Indeed, mismatch between the intrauterine and adult-life environments might explain much of the contemporary diabetes epidemic in several developing countries. For example, political and socioeconomic upheaval in Cambodia in 1975–79 resulted in severe undernutrition. King and colleagues[66] subsequently reported, in the setting of recent economic development and improved nutrition, the emergence of type 2 diabetes in Cambodia at rates similar to those in developed nations such as Australia.

These historical examples show the potential effect that famines, natural disasters, and malnutrition can have on trends in type 2 diabetes many decades after the events.[59–61] From a future perspective, current famine conditions, such as those in the Horn of Africa, could result in similar scenarios in 30 or 40 years' time.

With the evolving diabetes epidemic, particularly in populations at high risk of type 2 diabetes, gestational diabetes is becoming more prevalent and could further fuel the increase in diabetes prevalence.[67] In Pima Indians in the USA, individuals who were exposed to gestational diabetes in utero had a higher risk of the development of diabetes and obesity than did their unexposed siblings,[68] indicating that non-genetic, pregnancy-specific factors are important in linking of gestational diabetes and type 2 diabetes in offspring. Intrauterine hyperglycaemia causes fetal hyperinsulinaemia, which results in excess fetal growth. Epigenetic mechanisms might, once again, be an important mediator of this process.[63] Abnormal glucose tolerance during pregnancy affects both mothers and their offspring, with both at high risk of the later development of obesity, metabolic syndrome, and type 2 diabetes.

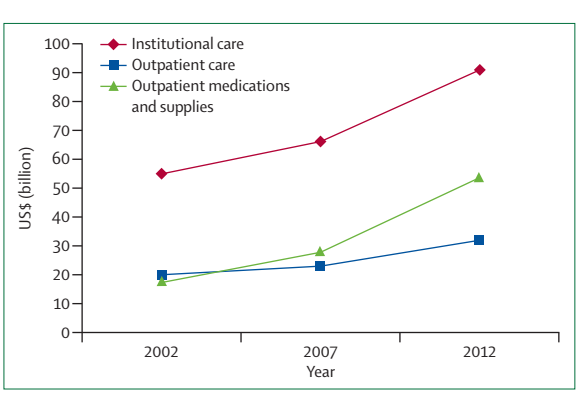

Figure 3: **US health-care expenditure in 2002–12 attributable to diabetes by cost component**[71,72]

The cost of diabetes and its complications

The economic effect of diabetes is enormous. In 2010, global health expenditure attributable to diabetes was estimated to be US$376 billion—that is, 12% of all global health expenditure.[69] In the USA in 2012, the direct medical cost of diabetes was $176 billion.[70] Health-care expenditure attributable to diabetes by cost component for the USA for 2002–12 is shown in figure 3. Expenditure attributable to outpatient medications and supplies increased from about $18 billion to $50 billion,[71,72]

providing an example of the increase in the cost of diabetes in a developed country. Information relating to costs in low-income and middle-income countries is sparse but urgently needed. Findings from a study[73] from China, albeit with some stated limitations, showed that the direct medical costs of type 2 diabetes and its complications were estimated at $26 billion in 2007, and they were projected to increase to $47·2 billion by 2030.

Expenditure attributable to diabetes varies hugely by region and national income.[69] More than 90% of global health expenditure on diabetes is in the world's richest countries: 57% in North America, 28% in Europe, and 10% in the western Pacific. Countries in the eastern Mediterranean, Middle East, sub-Saharan Africa, South America, Central America, and southeast Asia account for only 5% of global health expenditure attributable to diabetes, despite high prevalence of diabetes in many countries in these regions. Health expenditure attributable to diabetes (per person with diabetes per year) ranges from about $5800 in North America to about $50 in southeast Asia, a difference of more than 100 times.

Not surprisingly, the way in which money for diabetes is spent also differs drastically by region and national income.[74] In developed countries, only about a quarter of medical spending on diabetes is for control of blood glucose concentrations. Three-quarters of expenditure is for other medical care, including the treatment of complications and comorbidities, the most expensive being cardiovascular and renal disease. In developing countries, roughly half of medical spending is for control of blood glucose concentrations. In the poorest countries, more than half of annual health spending on diabetes is for medications that lower blood glucose concentrations to prevent life-threatening hyperglycaemia.[74]

The prospect for the future global economic burden of diabetes in developed countries is very worrying. In the USA, direct medical expenditure attributable to diabetes almost doubled from $92 billion in 2002 to $176 billion in 2012.[70,71] Some of this rise resulted from the increase in the number of people with diabetes, ageing of the population with diabetes, and inflation in medical costs. A substantial proportion was also due to greater use of new and expensive drugs and treatments for complications and comorbidities. Because the number of expensive diabetes drugs and treatments is increasing, and health expenditures increase with economic development, a future upsurge in health expenditure attributable to diabetes in developing countries is very probable and of substantial concern.

By 2030, estimated global health expenditure attributable to diabetes is expected to reach between $490 billion and $893 billion, an increase of 30–34% from 2010.[69] The projected increase in expenditures over the 20 years is 27% in developed countries and 67% in developing countries. These estimates are, however, based on the assumption that country-level, per-person health expenditure for diabetes will remain constant. For the reasons we have discussed, per-person health expenditure will almost certainly increase more than projections have suggested in both developed and developing countries.

Economic development is associated with increased per-person health-care expenditure, as has been the case with treatment for end-stage renal disease.[75,76] In 2004, roughly half of all patients undergoing dialysis in the world lived in North America and Europe. The prevalence of the need for dialysis was 1030 per million people in North America, and 400 per million in Europe. Globally, the prevalence of dialysis was 215 per million, with rates as low as 65 per million in Africa and 60 per million in Asia (excluding Japan).

An analysis of dialysis rates and national economic strengths expressed as per-person gross domestic product (GDP) suggested that economic factors impose restrictions on dialysis treatment in countries with per-person GDP of less than about $10 000 per year (figure 4).[75,76] In countries with per-person GDP above this value, factors other than economic wealth seem to determine the prevalence of treated end-stage renal disease. These factors include the prevalence of diabetes and the incidence of end-stage renal disease.

The challenge for the future is enormous, because economic development and increased access to care will lead to a massive increase in treatment, and contribute to a pronounced and probably unsustainable increase in health expenditure attributable to diabetes and its complications. This economic disaster will affect both developed and developing countries. Cost-effective interventions to delay or prevent the development of diabetes, its complications, and comorbidities are urgently needed to curtail the growing economic burden of diabetes.[77]

Prevention of diabetes: challenges ahead

Strategies for prevention of type 2 diabetes are well developed in some settings, but predominantly in developed nations. Lifestyle intervention has been effective

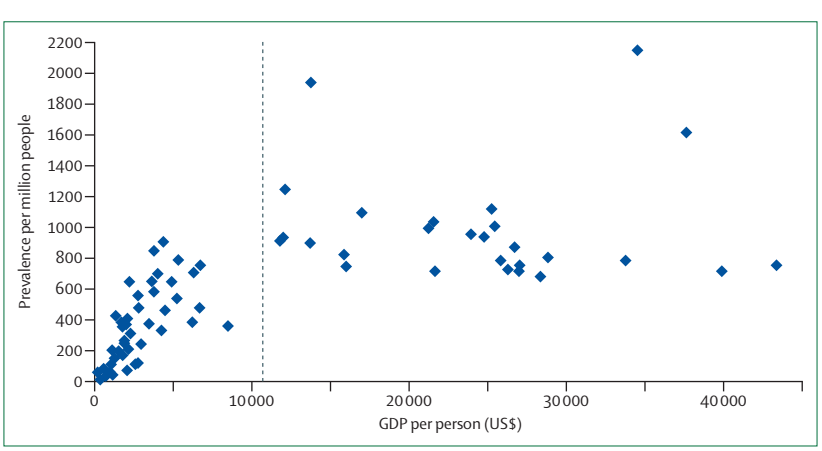

Figure 4: **Prevalence of treated end-stage renal disease in 2005 versus economic wealth in the 75 countries with the largest populations of patients with the disorder**
The dashed line shows the boundary between high-income and low-income or middle-income countries as classified by the World Bank.[76]

in several countries, but its success depends on uptake of intervention programmes and on compliance.[78–80] These barriers are not trivial, and the strategies used to overcome them might not be practicable in many low-income and middle-income countries. When diabetes prevention programmes developed from successful clinical trials have been implemented in real-world settings, uptake has generally been too low to have substantial effects on population levels of diabetes.[81,82] An urgent priority is to identify ways to effectively engage people at risk of diabetes. Long-term sustainability is also a concern.

Ideally, diabetes intervention should take a multipronged approach and should include individual lifestyle-based prevention, community initiatives in schools and workplaces, and regulatory changes to the food supply and urban planning. Furthermore, evidence is emerging that early life effects, particularly in utero, could strongly affect the risk of type 2 diabetes in adult life. Thus, the antecedents of the diabetes epidemic and approaches to prevention need to include a new and major focus on not only on the effect of fetal nutrition during pregnancy, but also suboptimal nutrition postnatally and in the first few years of life.[83]

Gestational diabetes has important implications for prevention of type 2 diabetes and control of the diabetes epidemic. Hyperglycaemia could cause epigenetic changes, which might be intergenerational.[63,84] The vicious cycle of diabetes begetting diabetes needs to be broken with effective prevention and intervention strategies. Measures are needed not only to improve the management of glucose intolerance during pregnancy, but also to ensure good prepregnancy education and planning to avoid environmental and behavioural exposures (nutritional, tobacco, or alcohol related), and other potential risks such as pollutants in food and toxicants in food packaging.[85]

Prevention of complications from diabetes is imperative, especially in under-resourced settings. Findings from our study[31] in Mauritius showed the effect of diabetes on mortality: over a 15-year follow-up, risk of death from any cause was two to three times higher in people with diabetes than in those without. Because the ethnic distribution of Mauritians corresponds to that of two-thirds of the global population, these findings suggest that diabetes will have a large effect on premature morbidity and mortality (and associated costs) worldwide.

A review[86] of 12 economic analyses in nine countries showed that, in 11 analyses, lifestyle interventions were cost effective or even cost saving for diabetes prevention. Economic analyses have further shown that glycaemic control and intensive management of blood pressure and lipids are cost effective for the prevention of diabetic complications.

Search strategy and selection criteria

We searched the scientific literature and other data sources regarding global diabetes incidence for articles that we judged to be important and timely contributions to the topics addressed in this Review. Our reference list was modified on the basis of comments from peer reviewers.

Conclusions

Type 2 diabetes is one of the great health-care challenges of the 21st century. Over the past two decades, diabetes has become an increasing threat not only in developed but also in developing countries. Diabetes can adversely affect productivity through premature morbidity and mortality, and its effects will probably become even more serious because the disorder is beginning to affect younger generations. The main effect will be in disadvantaged minority ethnic groups and in developing nations, where some of the highest prevalence of diabetes occurs.

In the absence of sustainable and affordable interventions, the frequency of both microvascular and macrovascular complications will increase globally. Prevention efforts should be widened to focus on prevention of gestational diabetes and subsequent intergenerational effects. Thus, prevention of diabetes, its complications, and associated disorders, such as cardiovascular disease, should be an essential component of future public health strategies for all countries.

Demographic conditions can profoundly affect diabetes prevalence and incidence. As we have noted, diabetes incidence decreased during World War 2. Recent increases in type 2 diabetes have occurred during periods of sustained economic growth in many nations. Paradoxically, the present situation of economic uncertainty, if sustained, could determine future trends in rates of diabetes rather than conventional intervention measures. Also, the contemporary famine conditions in countries from the Horn of Africa could presage a diabetes epidemic decades in the future, should economic conditions in this region improve.

Contributors

PZZ wrote the Review. DJM, JES, and WHH reviewed, edited, and provided intellectual input to the content and structure.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This Review was supported partly by the Victorian Government's OIS Program. JES is supported by a National Health and Medical Research Council fellowship (586623). WHH is supported by Grant Number P30DK092926 (MCDTR) from the National Institute of Diabetes and Digestive and Kidney Diseases. We thank David Whiting (NHS Medway, Rochester, UK), Leonor Guariguata (International Diabetes Federation, Brussels, Belgium), and the International Diabetes Federation for access to the latest global predictions data for diabetes, and to Assam El Osta (Baker IDI Heart & Diabetes Institute, Melbourne, VIC, Australia), Mark Cooper (Baker IDI Heart & Diabetes Institute, Melbourne, VIC, Australia), and Sir Peter Gluckman (Liggins Institute, University of Auckland, New Zealand) for their comments on the Review.

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