The Changing Nature of Mortality and Morbidity in Patients with Diabetes

Jonathan Pearson-Stuttard, FRSPH, MD[a,b,c,d,*],
James Buckley, MPH[a,b], Meryem Cicek, MPH[e],
Edward W. Gregg, PhD[a,b]

KEYWORDS

- Diabetes epidemiology • Diversification of mortality • Diversification of morbidity
- Multimorbidity • Chronic diseases

KEY POINTS

- The number of adults living with diabetes globally has increased substantially over the past 40 years.
- Death rates in high-income countries have reduced, driven in part by large declines in vascular disease mortality.
- There is evidence of a diversification of cause of death and complications in patients with diabetes.
- This has implications for prevention and management approaches targeting those with diabetes across the life course, which should reflect the breadth of conditions that these patients are at excess risk from.

BACKGROUND

The number of adults living with diabetes mellitus (DM) has increased globally over the past 40 years from 108 million to 422 million[1] owing to a rise in age-standardised prevalence, population growth, and aging. DM, therefore, represents a substantial challenge to individuals, health-care systems, and economies.

Individuals with DM are generally living longer, but an increasing portion of life lived is with DM,[2] which is likely to impact their morbidity profile. The high risk for those with

a Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK; b MRC Centre for Environment and Health, Imperial College London, Norfolk Place, London W2 1PG, UK; c Health Analytics, Lane Clark & Peacock LLP, 95 Wigmore Street, London W1U 1DQ, UK; d Northumbria Healthcare NHS Foundation Trust, North Shields NE27 0QJ, UK; e Department of Primary Care and Public Health, School of Public Health, Imperial College London, St Dunstan's Road, London W6 8RP, UK
* Corresponding author. Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London W2 1PG, UK.
E-mail address: j.pearson-stuttard@imperial.ac.uk

DM of developing and subsequently dying from vascular disease has been well characterized, and the accompanying high risk of ischemic heart disease (IHD),[3] stroke,[3,4] and renal[5] and neuropathic complications[6] has led to widely implemented specific secondary prevention guidelines for these traditional DM complications.[7]

However, there is now evidence that the spectrum of complications of diabetes is far more diverse than that portrayed by traditional complications. This diversification is likely due to several complex factors including increased longevity, changing risk factors, and changing treatment profiles. Exploring and quantifying these trends will be crucial to ensure that both policy and clinical care directed at those living with DM accurately reflects the breadth of health challenges they face and how this continues to evolve. We aim to review the evidence of this proposed diversification and outline the current knowledge in order to identify what this means for persons with DM and the public health efforts needed.

DISCUSSION
Trends in All-Cause Mortality

Estimating trends in all-cause and cause-specific mortality among those with diabetes provides insight into factors driving longevity, conditions contributing to excess risk of death in those with diabetes compared with those without to inform secondary prevention, and care pathway approaches. Despite the importance of this, only a few studies assess these trends in large diabetes populations.

Over the past two decades, all-cause mortality rates have generally declined steadily in persons with type 2 DM (T2DM) in populations across the United States (US),[8] Australia,[9] Canada,[9] and England,[10,11] with declines of between 30% and 35% over approximately 20-year periods in both US and England populations.[8,11] Similarly, a general reduction in the absolute gap in all-cause mortality rates between those with and without DM has also been found.[8] In the United States, the excess mortality in those with DM almost halved from 11.3 to 5.9 per 1000 person years in 1994 and 2015, respectively.[8] While similarly large declines in excess risk of mortality were found in Canada and the United Kingdom,[10] the reduction in excess risk was much more modest in men in England, with around a 10% decline from 12.3 to 11.1 deaths per 1000 from 2001 to 2018,[11] compared with a decline in excess risk from 14.5 to 10.8 per 1000 per year in women over the same time period.

Mixed Trends in Cause-Specific Mortality

The well-established association between diabetes and increased incidence of coronary heart disease (CHD) and stroke led[12] to wide implementation of specific secondary prevention guidelines for these traditional DM complications.[7] These efforts have likely contributed to large consistent declines in cardiovascular disease (CVD) mortality in those with DM across populations. Improvements in cancer mortality rates in those with DM, however, have generally been much more modest, compared with improvements in CVD mortality and compared with cancer mortality in those without DM. In women in England, for example, the average 10-year absolute change in mortality rates improved in vascular diseases by 6.6 deaths per 1000 people compared with no improvement (−0.1 deaths per 1000 people) in cancer mortality rates.[11] Death rates appear to be increasing in two specific causes in those with DM. Dementia mortality rates have increased several-fold in those with DM and at a worse rate than those without DM, whereas liver disease death rates worsened by approximately 23% in England DM populations compared with small declines in US populations.[8,11]

Diversification of Cause of Death

Alongside this decline in all-cause mortality, there has been a diversification in the causes of death in those with diabetes. This is reflected in the proportional contribution of different causes to the total. As the mortality burden attributed to vascular disease[8,9,11] has declined substantially over the past 30 years,[8,9,11] from 48% to 34% of all deaths in patients with DM in the United States and, with even larger reductions, from 44% to 24% in those with DM in England, other causes now take up a much larger proportional share (Fig. 1). The portion of deaths due to cancer has remained stable in US DM populations, with nonvascular, noncancer causes of death increasing, whereas deaths due to cancer increased in England from 22% to 28% over an 18-year period, with similar findings in Australia. Most striking in England is that this transition of mortality burden away from vascular diseases led to cancers being both the leading cause of death and the leading contributor to excess mortality risk in those with DM compared with those without,[11] with an excess cancer mortality risk of 4.5 per 1000 per year compared with an excess vascular of mortality risk 3.2 per 1000 per year in 2018.

There are only limited estimates of trends in causes of death in DM populations, and those that exist tend to be from high-income countries, with much fewer data on mortality trends in low- and middle-income countries (LMICs), which now bear the majority of the global diabetes burden. New data, however, are increasingly suggest that as individuals are living longer with DM, they are experiencing a diversification in cause of death away from traditional complications of DM such as IHD and stroke. This suggests that secondary prevention measures that have targeted vascular risk factors over past decades, along with population improvements in some key behavioral risk factors such as trans fats, blood pressure, and cholesterol, have been effective. However, in order to reduce the DM-related excess mortality risk further, we must widen the targeted preventative measures for those with DM to reflect the spectrum of conditions they are at increased risk of dying from and developing throughout the life course.
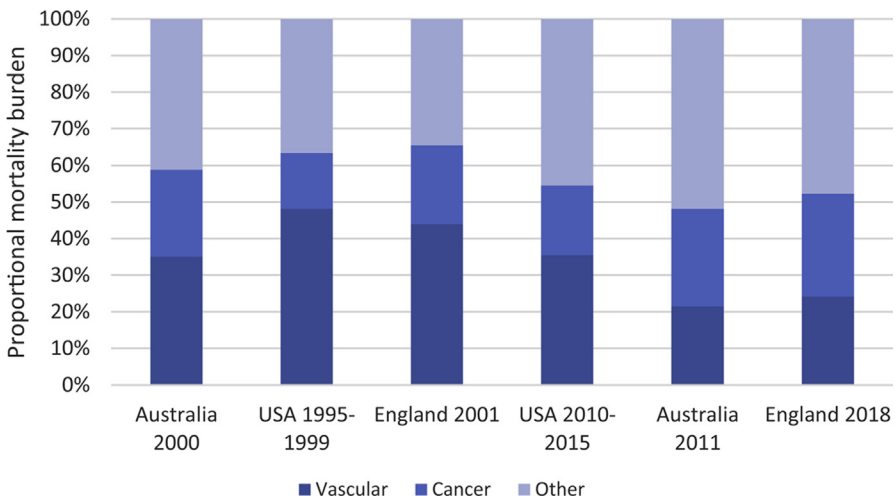
Fig. 1. Proportional mortality burden in those with diabetes attributable to vascular disease, cancers, or other disease in the United States, Australia, and England at time points over the past 25 years. (*Data from* Refs.[8,9,11])

DYNAMICS AND DIVERSIFICATION IN DIABETES-RELATED COMPLICATIONS

Diabetes complications have been traditionally classified into microvascular complications (eg, nephropathy, neuropathy, retinopathy), macrovascular complications (eg, stroke, CHD, peripheral vascular disease), and based on acute and chronic complications.[13] However, data from clinical settings have regularly shown that diabetes has far more diverse and wide-ranging effects on multiple organ systems than reflected in traditional complications. Furthermore, many of the most serious outcomes, such as lower extremity amputation (LEA), result from multiple simultaneous etiologic pathways.

Long-Term Trends in Incidence

There is now evidence from several population-based studies that the changing aspects of mortality among diabetes populations described previously are accompanied by, and possibly contributors to, changes in the spectrum of diabetes complications. In the United States, the incidence of diabetes-related complications as a whole declined by about half over 20 years, from 1990 to 2010.[6,14] Although there were reductions across a wide range of acute and chronic complications, the magnitude of decline was far greater for macrovascular diseases, particularly acute myocardial infarction (AMI), with decline by more than two-thirds over 2 decades, and stroke, hyperglycemic death, and LEAs, which declined by about half. The magnitude of decline was more modest, but still significant for end-stage renal disease (ESRD), which declined by about 30%. Importantly, the declines in diabetes-related complications were largely driven by older adults (aged >65 years) and only modest in young adults. This differential narrowed the age-related difference and the relative risk of most complications associated with age.

The differential trends in diabetes complications as per age and type have had three important effects on the character of population-wide diabetes-related complications in the United States. First, the age distribution of those with diabetes-related morbidity has shifted downward, such that persons younger than 65 years now account for about 90% of acute complication events, half of all events of microvascular complications, and 40% of all events of macrovascular disease.[6] Middle-aged adults now account for a third of strokes and more than half of amputations. Second, renal disease now takes up a greater proportion of all complications. This may also be true for microvascular disease complications in general, except that the lack of population-based data on incidence of retinopathy and neuropathy leaves this overall status of diabetes-related microvascular disease in the population unclear. A third by-product is that the combination of declining macrovascular disease complications and all-cause mortality, and perhaps a broader range of comorbid conditions, is permitting individuals with DM to live longer and develop second events. In the United States, rates of infections and cancers have not declined, and rates of other conditions not traditionally associated with diabetes, including chronic pulmonary disease and liver disease, have increased.[8] Furthermore, there is no clear evidence that levels of physical disability have declined.[14]

Similar trends in the incidence of LEA, CVD, and CVD mortality have been observed in several other countries of the world, most notably in Northern Europe.[15] A scoping review of international trends in diabetes complications revealed similar declines as those seen in the United States, Sweden, and South Korea and slightly more modest changes in Spain and the United Kingdom.[15] The review of the trends in LEAs has revealed declines in more than a dozen countries globally of varying magnitude both stronger and weaker than that seen in the United States. Reviews of ESRD have observed steady increases in several countries of the world but are based on a denominator of the general population, which partly reflects the growth in prevalence. There were no discernible variation in the magnitude of differences by region or specific country that could be

inferred from these reviews because of the different metrics and population character-istics and because intervening factors are generally not assessed in surveillance-based analyses. However, it is noteworthy that virtually all the population-based studies of DM-related complications have been conducted in high-income countries of Europe, North America, or Asia. We are not aware of published population-based studies that provided comparative rates of complications in other major high-risk regions of the world for diabetes, including the Middle East/North Africa, India, China, or Latin America.

The factors driving trends are unclear because direct analyses to identify driving factors have not been conducted. Concurrent surveillance data revealed steady im-provements in HbA1c levels, blood pressure, and lipid levels in the general population in the United States and other countries, accompanying a general proliferation of integrated care to deliver preventive care practices and early screening for complica-tions. However, the factors that affect trends in the population are largely speculative because direct analyses have not been conducted. Most importantly, however, even at the time of the lowest overall rates of diabetes complications in the United States—around 2012—only a small minority of patients get all recommended preventive care practices, indicating there is an enormous opportunity to reduce diabetes-related morbidity through better implementation of evidence-based practices.

A recent update of rates from 2010 to 2018 raised concern about a potential resur-gence of diabetes complications, particularly in young adult populations with T2DM.[16] After the year 2010, rates of LEA and acute hyperglycemia increased by almost 50% among young patients (aged 20–44 years) along with smaller increases in rates of ESRD, AMI, and stroke. Increases in LEA, acute hyperglycemia, and stroke also increased in middle-aged (aged 45–64 years) US adults. Although rates of complications did not increase in older adults, the long-term improvements in all complications stalled after 2010. The explanations for this apparent reversal remain unclear, as to whether they are being paralleled by other countries. These findings paralleled other observations of increases in hospitalizations for infections and acute hyperglycemia.[17–19] Increasing duration of disease, stalled improvements in preventive care practices, and socioeco-nomic disparities related to the great recession seem to be the most likely factors.

DIABETES-RELATED MULTIMORBIDITY
Future of Diabetes-Related Multimorbidity

Improvements in secondary and tertiary prevention and related declines in mortality, combined with the diversification of complications, have driven a concern and emphasis in the diabetes-related multimorbidity. Multimorbidity is the coexistence of two or more chronic conditions that often produce cumulative adverse health effects. Multimorbidity is commonly quantified as descriptive estimations of disease combinations, using severity-weighted indices such as Charlson and Elixhauser indices, or as clusters. The commonest comorbidities in those with DM are hypertension, depression, coronary heart disease, asthma, and chronic kidney disease (CKD).[20] As age and relative depri-vation are the leading drivers of multimorbidity,[21] there is concern that continued aging of the population will lead to an expansion of diabetes-related multimorbidity over the next decade[22] and that this is likely to be felt most intensely in LMICs.[23] Despite the increasing awareness of multimorbidity as an increasingly urgent challenge, there is currently sparse detail to inform specific measures to address this.

Traditional, Emerging, and Other Complications

DM-related multimorbidity can be categorized into three general groups; traditional (concordant) complications, emerging complications, and other (discordant)

comorbidities. Traditional complications—acute metabolic decompensation (hypo-glycemic and hyperglycemic episodes/crises), macrovascular conditions, and micro-vascular conditions—have been established for some time, and there are specific secondary prevention measures[7] in place for those with DM in order to mitigate this excess risk. Incidence of most of these traditional complications has declined, whereas hosptilizations for hypoglycaemic episodes have increased in young and middle-aged adults over recent decades.[24] Other vascular conditions such as heart failure are common in the T2DM population, with prevalence estimates of 2.7% to 3.6% at diagnosis.[20] There are several emerging conditions that have an increasing body of evidence to suggest a causal association with DM. Those with DM tend to have an increased risk of both signal[25] and common infections,[26] liver disease,[27] dementia,[28] and some site-specific cancers. Those with DM are estimated to have between a 1.5- and 2.5 times as high risk of dementia than those without DM, while associations are increasingly clear for six common cancers—breast, endometrial, liver, colorectal, pancreas, and gallbladder.[29] Although this is estimated to account for nearly 300,000 cancer cases annually,[30] the etiological mechanism remains unclear; hence, there are no specific prevention measures in place to reduce this excess risk.

In addition to these traditional and emerging complications, whereby an etiological link with DM is proposed, there are other conditions that appear to be more prevalent in those with DM, even if there are no proposed etiological links. This other group includes a much broader set of discordant conditions that have a considerable impact on quality of life, physical functioning, and independence later in life. These conditions include mental illnesses such as depression and anxiety,[15] respiratory conditions,[31,32] and musculoskeletal disorders.[33]

Depression is a very common discordant diabetes comorbidity that is illustrative of the increasing coprevalence of physical and mental health chronic conditions with onset in young and middle-aged adults. The primary link between diabetes and depression may be through common but distant third-degree factors such as correlated hormonal effects and inflammation. Depression is associated with lower quality of life and premature mortality in those with DM,[34,35] with an increasing consensus that this increased risk should be reflected in clinical care pathways.[35–38] However, similar to those emerging complications, we currently lack granular detail about the epidemiology of these comorbidities to inform specific action.

Who is at Risk of Diabetes Multimorbidity?

Age and relative deprivation are the leading drivers of multimorbidity in the general population, and the same appears to be true in those with DM. Although the burden of comorbidities appears similar across sex groups, age affects both the likelihood and types of multimorbidity. The number of comorbidities accumulated increases in those with DM as individuals age and as the duration of DM increases[12] with clear age-related comorbidity profiles, such as gastritis and duodenitis (18- to 39-year-olds), tuberculosis and hepatitis (30- to 49-year-olds), frailty and dementia ($\geq$80-year-olds), and diversity of clusters increasing with age.[39] As traditional DM complications are more common among people with lower socioeconomic status,[40,41] it is perhaps unsurprising that multimorbidity is higher in more deprived DM groups.[20] In such groups, CHD and asthma were more prevalent, which is suggestive of the role of behavioral risk factors such as smoking or alcohol consumption in comorbidity profiles in those with DM.[20,35] Ethnicity is likely to impact risk and patterns of comorbidity in those with DM too. While there is scarce evidence currently estimating this, Black and Asian individuals are 2.36 and 1.1 times more likely to have poor glycemic control than white individuals in the United Kingdom,[41] which could be expected to impact the risk of vascular

comorbidities and events. Similarly, early evidence suggests that non-Hispanic blacks and Hispanics bear the greatest burden of multimorbidity in the United States.[42–44]

Understanding How Conditions Cluster in Individuals with Diabetes

Disease surveillance systems can be leveraged to understand the network of nonrandom predictable clusters that comprise multimorbidity in wider populations and those with specific index chronic conditions such as DM.[45,46] Some of the emerging research in this relatively new field has used prevalence-driven pairwise techniques, and disease pairs that show co-occurrence frequencies, which are higher than predicted in the population, are considered connected.[47–49] Hypertension was the single most common condition among multimorbid patients with T2DM in a large UK cohort, with a higher prevalence among women than among men (45.8% vs 42.8%).[20] Musculoskeletal conditions, obesity, and hyperlipidemia made up the top 5 most common coprevalent conditions.[47,49] In the DM population, hypertension and CKD have the highest age-standardized coprevalence rate, with 12.1% at the time of diagnosis, increasing to 21.5% 9 years later[20] (Fig. 2). When considering three comorbid conditions concurrently, CVD, hypertension, and arthritis were the most prevalent ones found in 9.9% of patients with T2DM.[47] Hypertension is consistently found in the majority of T2DM-multimorbidity clusters of 2,[20,39,47,48] 3,[47,48] 4[50], and 5[50] comorbidities in several studies. However, the temporal sequence of multimorbidity in these T2DM populations is not well characterized.

Approaches such as latent class analyses, agglomerative, divisive hierarchical clustering,[39,50–52] and network and graph theory[53–55] have begun to identify patterns of comorbidities and trajectories of patient outcomes within specific subgroups. Some initial findings are perhaps expected, such as middle-aged men with T2DM and disorders of lipid metabolism being at a higher risk of major macrocardiovascular conditions, suggesting that dyslipidemia control is particularly important.[39] However, among older patients with long T2DM duration, there were more novel findings, identifying a cluster of conditions comprising depression, dementia, and end-stage organ complications.[35,56] This aligns with the American Diabetes Association guidelines for depression and dementia screening in elderly patients.[57]
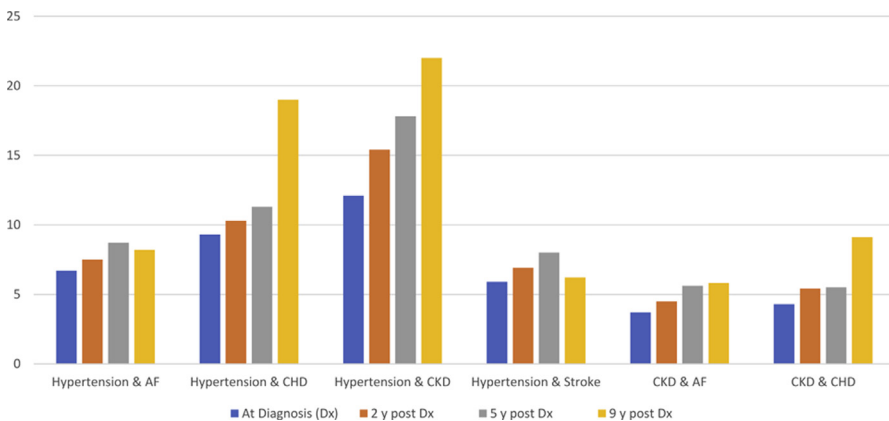
Fig. 2. Age-standardized prevalences of comorbidity combinations in those with diabetes at diagnosis and at 2, 5, and 9 years after diagnosis. (*Data from* Nowakowska M, Zghebi SS, Ashcroft DM, Buchan I, Chew-Graham C, Holt T, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. BMC Medicine. 2019;17(1):145.)

Viewing the Impact of Diabetes Holistically

As those with DM are living longer than in previous decades, an increasing proportion of them live in poor health from an increasingly diverse set of conditions. The impact of DM on patients' lives has evolved our view of not only how we manage their holistic health throughout the duration of their condition but also how we measure this impact. Mortality risk has long been the metric of choice for assessing impacts of interventions, whether therapeutics or care pathways, but as patterns of health and illness have changed, other measures become as important to patient groups such as functionality or life lived in good health. Health-care resource utilization is a broad measure that captures the holistic impact on patients and health systems, although it is not without its limitations such as coding incentives that may distort trends. This could, however, provide clues for initial efforts to alleviate multimorbidity in those with DM. Not only would this improve the lived experience for those with DM, but given the large and diverse impacts on the health and care system along with the wider economy,[58–61] this approach would benefit health systems too. Although the patterns and sequence of multimorbidity will be unique to those with DM, the structural challenges are not. Multimorbidity is increasing as populations age, and these patients account for a disproportionately high share of increased primary and secondary care visits and hospital admissions,[35,48,62] particularly in those with a mental health comorbidity.[63]

Initial evidence suggests that older patients with moderate to long DM duration (>5 years), with depression, dementia, and end-organ complications, tend to have the most total inpatient admissions, whereas younger women with short to moderate T2DM duration and a high psychiatric burden had the most Accident & Emergency (A&E) and outpatient clinic visits.[35] As with the comorbidity burden, health-care utilization is also influenced by ethnicity and deprivation.[41,64] Uncertainty remains with regard to the leading drivers of ill health and health care usage in those with DM and related comorbidities.[65] Along with most health-care structures and training, specialties often sit in silos, which is increasingly divergent from the multimorbid patients treated by health systems.

Improvements in treatment and prevention over past decades have led to substantial gains in longevity for those with DM; to compress morbidity over coming decades, a shift of approach from single disease to multimorbidity is required. Health surveillance systems along with administrative data sets hold a plethora of untapped opportunities to provide insight to guide meaningful changes to those living with DM. These are substantial challenges to researchers, clinicians, and policymakers alike, but if tackled effectively, it could put life back into years lived for those with DM and provide a lifeline to health systems struggling under aging populations to do more with less.

Substantial improvements in longevity for those with DM over recent decades have been accompanied by a diversification in mortality, complications, and comorbidities throughout the life course. In parallel to this, the heterogeneity of trajectories in those with diabetes based on risk factors and yet-unknown factors appears to be increasing too. Rather than disease- and organ-focused approaches, holistic patient-centered approaches will be required across preventative and clinical pathways to compress morbidity in those with DM to improve the trajectories for DM patients and health systems alike. Unfortunately, however, population-level estimates of these trends are generally limited to high-income countries, with no comparable data in LMICs, severely limiting our understanding of trends in outcomes in DM populations in the majority of the world. Future efforts should promote stronger surveillance in LMICs in order to address these evidence gaps.

CLINICS CARE POINTS

- The prevalence of diabetes has increased substantially globally, but all-cause death rates have declined in several diabetes populations, driven in part by large declines in vascular disease mortality.
- There has been a diversification in cause of death, whereby a larger share of deaths in those with diabetes being attributable to nonvascular conditions, whereas the share of cancer deaths has remained stable or even increased in some countries.
- A similar pattern has emerged in complications but with large differences across age-groups so that around 90% of all acute complication events are in those younger than 65 years, whereas this is true for half of all events of microvascular complications and 40% of all events of macrovascular disease.
- Alongside this diversification, the health trajectory among those with diabetes appears to become more heterogenous based on both known and yet-unknown risk factors.
- Prevention and management approaches to those with diabetes should take a more holistic approach to encompass the breadth of condition-specific excess risk that these patients face.

DISCLOSURE

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