The burden and risks of emerging complications of diabetes mellitus

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Abstract | The traditional complications of diabetes mellitus are well known and continue to pose a considerable burden on millions of people living with diabetes mellitus. However, advances in the management of diabetes mellitus and, consequently, longer life expectancies, have resulted in the emergence of evidence of the existence of a different set of lesser-acknowledged diabetes mellitus complications. With declining mortality from vascular disease, which once accounted for more than 50% of deaths amongst people with diabetes mellitus, cancer and dementia now comprise the leading causes of death in people with diabetes mellitus in some countries or regions. Additionally, studies have demonstrated notable links between diabetes mellitus and a broad range of comorbidities, including cognitive decline, functional disability, affective disorders, obstructive sleep apnoea and liver disease, and have refined our understanding of the association between diabetes mellitus and infection. However, no published review currently synthesizes this evidence to provide an in-depth discussion of the burden and risks of these emerging complications. This Review summarizes information from systematic reviews and major cohort studies regarding emerging complications of type 1 and type 2 diabetes mellitus to identify and quantify associations, highlight gaps and discrepancies in the evidence, and consider implications for the future management of diabetes mellitus.

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Diabetes mellitus is a common, albeit potentially devastating, medical condition that has increased in prevalence over the past few decades to constitute a major public health challenge of the twenty-first century[1]. Complications that have traditionally been associated with diabetes mellitus include macrovascular conditions, such as coronary heart disease, stroke and peripheral arterial disease, and microvascular conditions, including diabetic kidney disease, retinopathy and peripheral neuropathy[2] (FIG. 1). Heart failure is also a common initial manifestation of cardiovascular disease in patients with type 2 diabetes mellitus (T2DM)[3] and confers a high risk of mortality in those with T1DM or T2DM[4]. Although a great burden of disease associated with these traditional complications of diabetes mellitus still exists, rates of these conditions are declining with improvements in the management of diabetes mellitus[5]. Instead, as people with diabetes mellitus are living longer, they are becoming susceptible to a different set of complications[6]. Population-based studies[7–9] show that vascular disease no longer accounts for most deaths among people with diabetes mellitus, as was previously the case[10]. Cancer is now the leading cause of death in people with diabetes mellitus in some countries or regions (hereafter 'countries/regions')[9], and the proportion of deaths due to dementia has risen since the turn of the century[11]. In England, traditional complications accounted for more than 50% of hospitalizations in people with diabetes mellitus in 2003, but for only 30% in 2018, highlighting the shift in the nature of complications of this disorder over this corresponding period[12].

Cohort studies have reported associations of diabetes mellitus with various cancers, functional and cognitive disability, liver disease, affective disorders and sleep disturbance, and have provided new insights into infection-related complications of diabetes mellitus[13–17]. Although emerging complications have been briefly acknowledged in reviews of diabetes mellitus morbidity and mortality[11,17], no comprehensive review currently specifically provides an analysis of the evidence for the association of these complications with diabetes mellitus. In this Review, we synthesize information published since the year 2000 on the risks and burden of emerging complications associated with T1DM and T2DM.

Diabetes mellitus and cancer

The burden of cancer mortality

With the rates of cardiovascular mortality declining amongst people with diabetes mellitus, cancer deaths now constitute a larger proportion of deaths among this population in some countries/regions[8,9]. Although the proportion of deaths due to cancer appears to be

Key points

- With advances in the management of diabetes mellitus, evidence is emerging of an increased risk and burden of a different set of lesser-known complications of diabetes mellitus.
- As mortality from vascular diseases has declined, cancer and dementia have become leading causes of death amongst people with diabetes mellitus.
- Diabetes mellitus is associated with an increased risk of various cancers, especially gastrointestinal cancers and female-specific cancers.
- Hospitalization and mortality from various infections, including COVID-19, pneumonia, foot and kidney infections, are increased in people with diabetes mellitus.
- Cognitive and functional disability, nonalcoholic fatty liver disease, obstructive sleep apnoea and depression are also common in people with diabetes mellitus.
- As new complications of diabetes mellitus continue to emerge, the management of this disorder should be viewed holistically, and screening guidelines should consider conditions such as cancer, liver disease and depression.

stable, at around 16–20%, in the population with diabetes mellitus in the USA[7], in England it increased from 22% to 28% between 2001 and 2018 (REF.[9]), with a similar increase reported in Australia[8]. Notably, in England, cancer has overtaken vascular disease as the leading cause of death in people with diabetes mellitus and it is the leading contributor to excess mortality in those with diabetes mellitus compared with those without[9]. These findings are likely to be due to a substantial decline in the proportion of deaths from vascular diseases, from 44% to 24% between 2001 and 2018, which is thought to reflect the targeting of prevention measures in people with diabetes mellitus[18]. Over the same time period, cancer mortality rates fell by much less in the population with diabetes mellitus than in that without diabetes[9], suggesting that clinical approaches for diabetes mellitus might focus too narrowly on vascular complications and might require revision[19]. In addition, several studies have reported that female patients with diabetes mellitus receive less-aggressive treatment for breast cancer compared with patients without diabetes mellitus, particularly with regard to chemotherapy[20–22], suggesting that this treatment approach might result in increased cancer mortality rates in women with diabetes mellitus compared with those without diabetes mellitus. Although substantial investigation of cancer mortality in people with diabetes mellitus has been undertaken in high-income countries/regions, there is a paucity of evidence from low-income and middle-income countries/regions. It is important to understand the potential effect of diabetes mellitus on cancer mortality in these countries/regions owing to the reduced capacity of health-care systems in these countries/regions to cope with the combination of a rising prevalence of diabetes mellitus and rising cancer mortality rates in those with diabetes mellitus. One study in Mauritius showed a significantly increased risk of all-cause cancer mortality in patients with T2DM[23], but this study has yet to be replicated in other low-income and middle-income countries/regions.

Gastrointestinal cancers

Of the reported associations between diabetes mellitus and cancer (TABLE 1), some of the strongest have been demonstrated for gastrointestinal cancers.

Hepatocellular carcinoma. In the case of hepatocellular carcinoma, the most rigorous systematic review on the topic — comprising 18 cohort studies with a combined total of more than 3.5 million individuals — reported a summary relative risk (SRR) of 2.01 (95% confidence interval (CI) 1.61–2.51) for an association with diabetes mellitus[24]. This increased risk of hepatocellular carcinoma with diabetes mellitus is supported by the results of another systematic review that included case–control studies[25]. Another review also found that diabetes mellitus independently increased the risk of hepatocellular carcinoma in the setting of hepatitis C virus infection[26].

Pancreatic cancer. The risk of pancreatic cancer appears to be approximately doubled in patients with T2DM compared with patients without T2DM. A meta-analysis of 36 studies found an adjusted odds ratio (OR) of

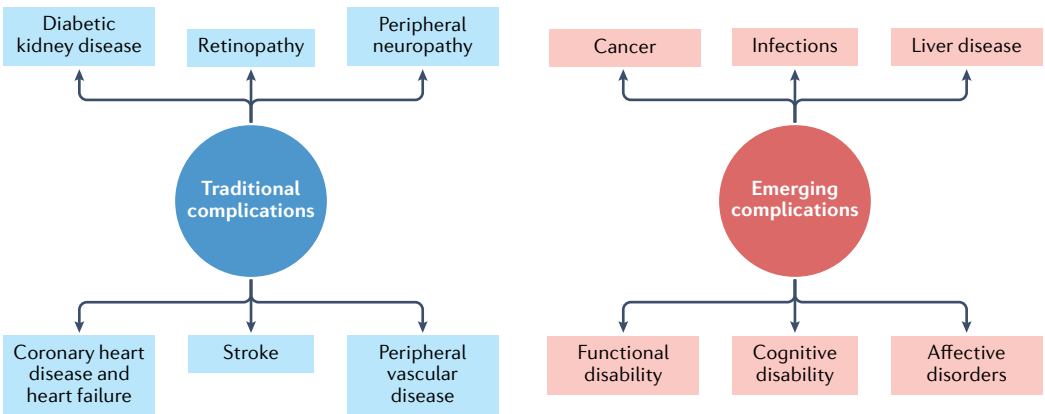

Fig. 1 | **Major traditional complications and emerging complications of diabetes mellitus.** The traditional complications of diabetes mellitus include stroke, coronary heart disease and heart failure, peripheral neuropathy, retinopathy, diabetic kidney disease and peripheral vascular disease, as represented on the left-hand side of the diagram. With advances in the management of diabetes mellitus, associations between diabetes mellitus and cancer, infections, functional and cognitive disability, liver disease and affective disorders are instead emerging, as depicted in the right-hand side of the diagram. This is not an exhaustive list of complications associated with diabetes mellitus.

Table 1 | **Summary of major systematic reviews and original studies reporting a cancer risk associated with diabetes mellitus**

Study	Diabetes mellitus type	Study type included (*n*)	Outcome	Risk associated with diabetes mellitus (95% confidence interval)
Wang et al.[a] (2012)[24]	All	Cohort (3,626,368[b])	Hepatocellular carcinoma	RR 2.01 (1.61–2.51)
El-Serag et al.[a] (2006)[25]	All	Cohort, cross-sectional (2,938,889[b])	Hepatocellular carcinoma	RR 2.5 (cohort studies) (1.9–3.2) and OR 2.5 (case–control) (1.8–3.5)
Huxley et al.[a] (2005)[27]	T2DM	Cohort, cross-sectional (9,220)	Pancreatic cancer	OR 1.82 (1.66–1.89)
	1–4 years duration			OR 2.05 (1.87–2.25)
	5–9 years duration			OR 1.54 (1.31–1.81)
	≥10 years duration			OR 1.51 (1.16–1.96)
Carstensen et al.[c] (2016)[30]	T1DM	Cohort (9,149)	Pancreatic cancer	HR 1.53 (males) (1.30–1.79) and HR 1.25 (females) (1.02–1.53)
Jiang et al.[a] (2011)[31]	All	Cohort (8,244,732[b])	Colorectal cancer	RR 1.27 (1.21–1.34)
Deng et al.[a] (2012)[33]	All	Cohort, cross-sectional (3,659,341)	Colorectal cancer	RR 1.26 (1.20–1.31)
De Bruijn et al.[a] (2013)[32]	All	Cohort, randomized controlled trials (1,930,309)	Colorectal cancer	HR 1.26 (1.14–1.40)
			Breast cancer	HR 1.23 (1.12–1.34)
Liao et al.[a] (2014)[34]	All	Cohort (5,302,259)	Endometrial cancer	RR 1.89 (1.46–2.45)
			Endometrial cancer disease-specific mortality	RR 1.32 (1.10–1.60)
Saed et al.[a] (2019)[35]	All	Cohort, cross-sectional (459,167[b])	Endometrial cancer	RR 1.72 (1.48–2.01)
Friberg et al.[a] (2007)[36]	All	Cohort, cross-sectional (96,003)	Endometrial cancer	RR 2.10 (1.75–2.53)
	T1DM			RR 3.15 (1.07–9.29)
Larsson et al.[a] (2007)[38]	T2DM	Cohort, cross-sectional (1,430,122[b])	Breast cancer	RR 1.20 (1.12–1.28)
Anothaisintawee et al.[a] (2013)[37]	All	Cohort, cross-sectional (1,090,503[b])	Breast cancer	OR 1.14 (1.09–1.19)
Boyle et al.[a] (2012)[39]	All	Cohort, cross-sectional (21,029[b])	Breast cancer (postmenopausal)	RR 1.15 (1.07–1.24)
Zhang et al.[a] (2017)[43]	All	Cohort (2,392,245[b])	Ovarian cancer	RR 1.32 (1.14–1.52)
Weng et al.[a] (2017)[44]	All	Cohort (3,708,313)	Ovarian cancer	RR 1.19 (1.06–1.34)
Wang et al.[a] (2020)[45]	All	Cohort, cross-sectional (6,036,434[b])	Ovarian cancer	RR 1.20 (1.10–1.31)
Lee et al.[a] (2013)[46]	All	Cohort, cross-sectional (1,707,359[b])	Ovarian cancer	RR 1.17 (1.02–1.33)
Bonovas et al.[a] (2004)[47]	All	Cohort, cross-sectional (890,678[b])	Prostate cancer	RR 0.91 (0.86–0.96)
Long et al.[a] (2012)[49]	All (Asia only)	Cohort, cross-sectional (1,751,274)	Prostate cancer	RR 1.31 (1.12–1.54)

HR, hazard ratio; OR, odds ratio; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. [a]Systematic review. [b]Total number of participants obtained through sum of individual study cohort sizes listed in tables or otherwise. [c]Original study.

1.82 (95% CI 1.66–1.89) for pancreatic cancer among people with T2DM compared with patients without T2DM[27] (TABLE 1). However, it is possible that these findings are influenced by reverse causality — in this scenario, diabetes mellitus is triggered by undiagnosed pancreatic cancer[28], with pancreatic cancer subsequently being clinically diagnosed only after the diagnosis of diabetes mellitus. Nevertheless, although the greatest risk (OR 2.05, 95% CI 1.87–2.25) of pancreatic cancer was seen in people diagnosed with T2DM 1–4 years previously compared with people without T2DM, those with a diagnosis of T2DM of more than 10 years remained at increased risk of pancreatic cancer (OR 1.51, 95% CI 1.16–1.96)[27], suggesting that reverse causality can explain only part of the association between T2DM and pancreatic cancer. Although T2DM accounts for ~90% of all cases of diabetes mellitus[29], a study incorporating data from five nationwide diabetes registries also reported an increased risk of pancreatic cancer amongst both male patients (HR 1.53, 95% CI 1.30–1.79) and female patients (HR 1.25, 95% CI 1.02–1.53) with T1DM[30].

Colorectal cancer. For colorectal cancer, three systematic reviews have shown a consistent 20–30% increased risk associated with diabetes mellitus[31–33]. One systematic review, which included more than eight million people across 30 cohort studies, reported an incidence SRR of 1.27 (95% CI 1.21–1.34) of colorectal cancer[31], independent of sex and family history (TABLE 1). Similar increases in colorectal cancer incidence in patients with diabetes mellitus were reported in a meta-analysis of randomized controlled trials (RCTs) and cohort studies[32] and in a systematic review that included cross-sectional studies[33].

Female-specific cancers

Endometrial, breast and ovarian cancers all occur more frequently in women with diabetes mellitus than in women without diabetes mellitus.

Endometrial cancer. For endometrial cancer, one systematic review of 29 cohort studies and a combined total of 5,302,259 women reported a SRR of 1.89 (95% CI 1.46–2.45) and summary incidence rate ratio (IRR) of 1.61 (95% CI 1.51–1.71)[34] (TABLE 1). Similar increased risks were found in two systematic reviews incorporating cross-sectional studies[35,36], one of which found a particularly strong association of T1DM (relative risk (RR) 3.15, 95% CI 1.07–9.29) with endometrial cancer.

Breast cancer. The best evidence for a link between diabetes mellitus and breast cancer comes from a systematic review of six prospective cohort studies and more than 150,000 women, in which the hazard ratio (HR) for the incidence of breast cancer in women with diabetes mellitus compared with women without diabetes mellitus was 1.23 (95% CI 1.12–1.34)[32] (TABLE 1). Two further systematic reviews have also shown this increased association[37,38].

The association of diabetes mellitus with breast cancer appears to vary according to menopausal status. In a meta-analysis of studies of premenopausal women with diabetes mellitus, no significant association with breast cancer was found[39], whereas in 11 studies that included only postmenopausal women, the SRR was 1.15 (95% CI 1.07–1.24). The difference in breast cancer risk between premenopausal and postmenopausal women with diabetes mellitus was statistically significant. The increased risk of breast cancer after menopause in women with diabetes mellitus compared with women without diabetes mellitus might result from the elevated concentrations and increased bioavailability of oestrogen that are associated with adiposity[40], which is a common comorbidity in those with T2DM; oestrogen synthesis occurs in adipose tissue in postmenopausal women, while it is primarily gonadal in premenopausal women[41]. Notably, however, there is evidence that hormone-receptor-negative breast cancers, which typically carry a poor prognosis, occur more frequently in women with breast cancer and diabetes mellitus than in women with breast cancer and no diabetes mellitus[42], indicating that non-hormonal mechanisms also occur.

Ovarian cancer. Diabetes mellitus also appears to increase the risk of ovarian cancer, with consistent results from across four systematic reviews. A pooled RR of 1.32 (95% CI 1.14–1.52) was reported across 15 cohort studies and a total of more than 2.3 million women[43] (TABLE 1). A SRR of 1.19 (95% CI 1.06–1.34) was found across 14 cohort studies and 3,708,313 women[44]. Similar risks were reported in meta-analyses that included cross-sectional studies[45,46].

Male-specific cancers: prostate cancer

An inverse association between diabetes mellitus and prostate cancer has been observed in a systematic review (RR 0.91, 95% CI 0.86–0.96)[47], and is probably due to reduced testosterone levels that occur secondary to the low levels of sex hormone-binding globulin that are commonly seen in men with T2DM and obesity[48]. Notably, however, the systematic review that showed the inverse association involved mostly white men (TABLE 1), whereas a systematic review of more than 1.7 million men from Taiwan, Japan, South Korea and India found that diabetes mellitus increased prostate cancer risk[49], suggesting that ethnicity might be an effect modifier of the diabetes mellitus–prostate cancer relationship. The mechanisms behind this increased risk in men in regions of Asia such as Taiwan and Japan, where most study participants came from, remain unclear. Perhaps, as Asian men develop diabetes mellitus at lower levels of total adiposity than do white men[50], the adiposity associated with diabetes mellitus in Asian men might have a lesser impact on sex hormone-binding globulin and testosterone than it does in white men. Despite the reported inverse association between diabetes mellitus and prostate cancer in white men, however, evidence suggests that prostate cancers that do develop in men with T2DM are typically more aggressive, conferring higher rates of disease-specific mortality than prostate cancers in men without diabetes mellitus[51].

An assessment of cancer associations

As outlined above, a wealth of data has shown that diabetes mellitus is associated with an increased risk of various cancers. It has been argued, however, that some of these associations could be due to detection bias resulting from increased surveillance of people with diabetes mellitus in the immediate period after diagnosis[52], or reverse causality, particularly in the case of pancreatic cancer[53]. However, neither phenomenon can account for the excess risks seen in the longer term. An Australian study exploring detection bias and reverse causality found that standardized mortality ratios (SMRs) for several cancer types in people with diabetes mellitus compared with the general population fell over time, but remained elevated beyond 2 years for pancreatic and liver cancers[54], suggesting that diabetes mellitus is a genuine risk factor for these cancer types.

A limitation of the evidence that surrounds diabetes mellitus and cancer risk is high clinical and methodological heterogeneity across several of the large systematic reviews, which makes it difficult to be certain of the effect size in different demographic groups. Additionally, many of the studies exploring a potential association between diabetes mellitus and cancer were unable to adjust for BMI, which is a major confounder. However, a modelling study that accounted for BMI found that although 2.1% of cancers worldwide in 2012 were attributable to diabetes mellitus as an independent risk factor, twice as many cancers were attributable to high BMI[55], so it is likely that effect sizes for cancer risk associated with diabetes mellitus would be attenuated after adjustment for BMI. Notably, however, low-income and middle-income countries/regions had the largest increase in the numbers of cases of cancer attributable to diabetes mellitus both alone and in combination with BMI[55], highlighting the need for public health intervention, given that these countries/regions are less equipped than high-income countries/regions to manage a growing burden of cancer.

As well as the cancer types outlined above, diabetes mellitus has also been linked to various other types of cancer, including kidney cancer[56], bladder cancer[57] and

haematological malignancies; however, the evidence for these associations is not as strong as for the cancers discussed above[58]. Diabetes mellitus might also be associated with other cancer types such as small intestine cancer, but the rarity of some of these types makes it difficult to obtain sufficient statistical power in analyses of any potential association.

Potential aetiological mechanisms

Several aetiological mechanisms that might be involved in linking diabetes mellitus to cancer have been proposed, including hyperinsulinaemia, hyperglycaemia, inflammation and cellular signalling mechanisms.

Hyperinsulinaemia. Most cancer cells express insulin receptors, through which hyperinsulinaemia is thought to stimulate cancer cell proliferation and metastasis[59]. Hyperinsulinaemia might also promote carcinogenesis through increased local levels of insulin-like growth factor 1 (IGF1), which has potent mitogenic and anti-apoptotic activities[60], owing to decreased levels of insulin-like growth factor binding proteins. As outlined above, people with diabetes mellitus show a strong risk of pancreatic and liver cancers; this increased risk might occur because insulin is produced by pancreatic β-cells and transported to the liver via the portal vein[61], thereby exposing the liver and pancreas to high levels of endogenous insulin[59].

Hyperglycaemia and inflammation. Hyperglycaemia can induce DNA damage[62], increase the generation of reactive oxygen species[63] and downregulate antioxidant expression[64], all of which are associated with cancer development. Inflammatory markers, including cytokines such as IL-6, appear to have an important role in the association between diabetes and cancer[65].

Cellular signalling mechanisms. Several cellular signalling components are common to the pathogenesis of T2DM and cancer. These include the mechanistic target of rapamycin (mTOR), a central controller of cell growth and proliferation; AMP-activated protein kinase, a cellular energy sensor and signal transducer[66]; and the phosphatidylinositol 3-kinase (PI3K)–AKT pathway, which transduces growth factor signals during organismal growth, glucose homeostasis and cell proliferation[67]. Dysregulation of any of these cellular signalling components or pathways could contribute to the development of cancer and metabolic disorders, including T2DM, and glucose-lowering drugs such as metformin have been associated with a reduction in cancer cell proliferation through effective inhibition of some of these components[68].

Diabetes mellitus and infections

Infection-related complications

Although infection has long been recognized as a complication of diabetes mellitus, an association between diabetes mellitus and infection has not been well documented in epidemiological studies[69]. Only in the past decade have major studies quantified the burden of infection-related complications in people with diabetes mellitus and explored the specific infections accounting for this burden. In a US cohort of 12,379 participants, diabetes mellitus conferred a significant risk of infection-related hospitalization, with an adjusted HR of 1.67 (95% CI 1.52–1.83) compared with people without diabetes mellitus[70] (TABLE 2). The association was most pronounced for foot infections (HR 5.99, 95% CI 4.38–8.19), with significant associations also observed for respiratory infection, urinary tract infection, sepsis and post-operative infection, but not for gastrointestinal infection, a category that included appendicitis and gastrointestinal abscesses but not viral or bacterial gastroenteritis. Interestingly, a report from Taiwan demonstrated an association between the use of metformin and a lower risk of appendicitis[71].

In an analysis of the entire Hong Kong population over the period 2001–2016, rates of hospitalization for all types of infection remained consistently higher in people with diabetes mellitus than in those without diabetes mellitus[72]. The strongest association was seen for hospitalization due to kidney infections, for which the adjusted RR was 4.9 (95% CI 3.9–6.2) in men and 3.2 (95% CI 2.8–3.7) in women with diabetes mellitus compared with those without diabetes mellitus in 2016 (TABLE 2). Diabetes mellitus roughly doubled the risk of hospitalization from tuberculosis or sepsis. The most common cause of infection-related hospitalization was pneumonia, which accounted for 39% of infections across the study period, while no other single cause accounted for more than 25% of infections across the same period. Pneumonia-related hospitalization rates increased substantially from 2001 to 2005, probably as a result of the 2003 severe acute respiratory syndrome (SARS) epidemic and the decreased threshold for pneumonia hospitalization in the immediate post-epidemic period. Rates for hospitalization for influenza increased from 2002 to 2016, possibly because of changes in the virus and increased testing for influenza. Declining rates of hospitalization for tuberculosis, urinary tract infections, foot infections and sepsis could be due to improvements in the management of diabetes mellitus.

Infection-related mortality rates were found to be significantly elevated among 1,108,982 Australians with diabetes mellitus studied over the period 2000–2010 compared with rates in people without diabetes mellitus[73]. For overall infection-related mortality, SMRs were 4.42 (95% CI 3.68–5.34) for T1DM and 1.47 (95% CI 1.42–1.53) for people with T2DM compared with those without diabetes mellitus (TABLE 2). Substantially higher infection-related mortality rates were seen in people with T1DM compared with those with T2DM for all infection types, even after accounting for age. Hyperglycaemia is thought to be a driver of infection amongst people with diabetes mellitus (see below)[73], which might explain the higher SMRs amongst people with T1DM, in whom hyperglycaemia is typically more severe, than in those with T2DM. The highest SMRs were seen for osteomyelitis, and SMRs for septicaemia and pneumonia were also greater than 1.0 for both types of diabetes mellitus compared with those without diabetes mellitus.

Table 2 | **Summary of major systematic reviews and original studies reporting an infection risk associated with diabetes mellitus**

Study	Diabetes mellitus type	Study type included (*n*)	Outcome	Risk associated with diabetes mellitus (95% confidence interval)
Fang et al.[a] (2021)[70]	All	Cohort (12,379)	Infection-related hospitalization	HR 1.67 (1.52–1.83)
			Hospitalization for foot infections	HR 5.99 (4.38–8.19)
Luk et al.[a] (2021)[72]	All	Cohort (6,164,082)	Hospitalization for kidney infection (male individuals)	RR 2.50 (1.70–3.50)
			Hospitalization for kidney infection (female individuals)	RR 2.10 (1.70–2.70)
			Hospitalization for tuberculosis (male individuals)	RR 2.20 (2.00–2.40)
			Hospitalization for tuberculosis (female individuals)	RR 2.10 (1.80–2.40)
			Hospitalization for sepsis (male individuals)	RR 2.30 (2.10–2.50)
			Hospitalization for sepsis (female individuals)	RR 2.30 (2.10–2.50)
Magliano et al.[b] (2015)[73]	T1DM	Cohort (85,144)	Infection-related mortality	SMR 4.42 (3.68–5.34)
			Pneumonia-related mortality	SMR 6.23 (4.30–9.00)
			Septicaemia-related mortality	SMR 10.00 (6.70–14.90)
			Osteomyelitis-related mortality	SMR 16.30 (5.20–50.40)
Magliano et al.[a] (2015)[73]	T2DM	Cohort (1,023,838)	Infection-related mortality	SMR 1.47 (1.42–1.53)
			Pneumonia-related mortality	SMR 1.20 (1.20–1.30)
			Septicaemia-related mortality	SMR 1.80 (1.70–2.00)
			Osteomyelitis-related mortality	SMR 3.50 (2.90–4.30)
Martin et al.[b] (2016)[74]	All	RCTs, cohort, cross-sectional (32,067); 90 studies	Surgical site infection	OR 1.77 (adjusted measures; 1.13–2.78); heterogeneity (I2) = 71%
McGurnaghan et al.[a] (2021)[79]	All	Cohort (5,463,300)	Fatal or critical care unit-treated COVID-19	OR 1.40 (1.30–1.49)
Rawshani et al.[a] (2021)[80]	T1DM	Cohort (44,639)	COVID-19 hospitalization	HR 2.10 (1.72–2.57)
	T2DM	Cohort (411,976)		HR 2.22 (2.13–2.32)
You et al.[a] (2020)[81]	T2DM	Cohort (5,473)	Intensive care unit-treated COVID-19	OR 1.59 (1.02–2.49)
Moon et al.[a] (2020)[82]	All	Cohort (5,307)	Oxygen treatment in COVID-19	OR 1.35 (1.10–1.66)
			Ventilator requirement in COVID-19	OR 1.93 (1.28–2.92)

COVID-19, coronavirus disease 2019; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SMR, standardized mortality ratio. [a]Original study. [b]Systematic review.

Post-operative infection

Post-operative infection is also an important complication of diabetes mellitus. In a meta-analysis, diabetes mellitus was found to be associated with an OR of 1.77 (95% CI 1.13–2.78) for surgical site infection across studies that adjusted for confounding factors[74] (TABLE 2). The effect size appears to be greatest after cardiac procedures, and one US study of patients undergoing coronary artery bypass grafting found diabetes mellitus to be an independent predictor of surgical site infection, with an OR of 4.71 (95% CI 2.39–9.28) compared with those without diabetes mellitus[75]. Risks of infection of more than threefold were reported in some studies of gynaecological[76] and spinal surgery[77] in people with diabetes mellitus compared with those without diabetes mellitus. Increased risks of infection among people with diabetes mellitus were also observed in studies of colorectal and breast surgery and arthroplasty, suggesting that the association between diabetes mellitus and post-operative infection is present across a wide range of types of surgery[74].

Respiratory infections

The incidence of hospitalizations due to respiratory infections among people with diabetes mellitus was increasing substantially even before the onset of the coronavirus disease 2019 (COVID-19) pandemic, probably owing to increased life expectancy in these patients as well as an increased likelihood of them being hospitalized for conditions such as respiratory infections, which occur mostly in older age[12]. This rising burden of respiratory infection, in combination with the rising prevalence of diabetes mellitus, highlights the importance of addressing the emerging complications of diabetes mellitus to minimize impacts on health-care systems in current and future global epidemics.

COVID-19. Although diabetes mellitus does not appear to increase the risk of becoming infected with COVID-19 (REF.[78]), various population-based studies have reported increased risks of COVID-19 complications among people with diabetes mellitus. In a study of the total Scottish population, people with diabetes mellitus were found to have an increased risk of fatal or critical care unit-treated COVID-19, with an adjusted OR of 1.40 (95% CI 1.30–1.50) compared with those without diabetes mellitus[79] (TABLE 2). The risk was particularly high for those with T1DM (OR 2.40, 95% CI 1.82–3.16)[79]. Both T1DM and T2DM have been linked to a more than two-fold increased risk of hospitalization with COVID-19 in a large Swedish cohort study[80]. In South Korean studies, T2DM was linked to intensive care unit admission among patients with COVID-19 infection[81], and diabetes mellitus (either T1DM or T2DM) was linked to a requirement for ventilation and oxygen therapy[82] in patients with COVID-19. Diabetes mellitus appears to be the primary predisposing factor for opportunistic infection with mucormycosis in individuals with COVID-19 (REF.[83]). The evidence for diabetes mellitus as a risk factor for post-COVID-19 syndrome is inconclusive[84,85]. Interestingly, an increase in the incidence of T1DM during the COVID-19 pandemic has been reported in several countries/regions[86], and some data suggest an increased risk of T1DM after COVID-19 infection[87], but the evidence regarding a causal effect is inconclusive.

Pneumonia, MERS, SARS and H1N1 influenza. The data regarding diabetes mellitus and COVID-19 are consistent with the published literature regarding other respiratory infections, such as pneumonia, for which diabetes mellitus has been shown to increase the risk of hospitalization[88] and mortality[88], with similar effect sizes to those seen for COVID-19, compared with no diabetes mellitus. Diabetes mellitus has also been also linked to adverse outcomes in people with Middle East respiratory syndrome (MERS), SARS and H1N1 influenza[89–92], suggesting that mechanisms specific to COVID-19 are unlikely to be responsible for the relationship between diabetes mellitus and COVID-19. Unlike the case for COVID-19, there is evidence that people with diabetes mellitus are at increased risk of developing certain other respiratory infections, namely pneumonia[93] and possibly also MERS[94].

Potential aetiological mechanisms

The mechanisms that might link diabetes mellitus and infection include a reduced T cell response, reduced neutrophil function and disorders of humoral immunity.

Mononuclear cells and monocytes of individuals with diabetes mellitus secrete less IL-1 and IL-6 than the same cells from people without diabetes mellitus[95]. The release of IL-1 and IL-6 by T cells and other cell types in response to infection has been implicated in the response to several viral infections[96]. Thus, the reduced secretion of these cytokines in patients with diabetes mellitus might be associated with the poorer responses to infection observed among these patients compared with people without diabetes mellitus.

In the context of neutrophil function, hyperglycaemic states might give rise to reductions in the mobilization of polymorphonuclear leukocytes, phagocytic activity and chemotaxis[97], resulting in a decreased immune response to infection. Additionally, increased levels of glucose in monocytes isolated from patients with obesity and/or diabetes mellitus have been found to promote viral replication in these cells, as well as to enhance the expression of several cytokines, including pro-inflammatory cytokines that are associated with the COVID-19 'cytokine storm'; furthermore, glycolysis was found to sustain the SARS coronavirus 2 (SARS-CoV-2)-induced monocyte response and viral replication[98].

Elevated glucose levels in people with diabetes mellitus are also associated with an increase in glycation, which, by promoting a change in the structure and/or function of several proteins and lipids, is responsible for many of the complications of diabetes mellitus[99]. In people with diabetes mellitus, antibodies can become glycated, a process that is thought to impair their biological function[100]. Although the clinical relevance of this impairment is not clear, it could potentially explain the results of an Israeli study that reported reduced COVID-19 vaccine effectiveness among people with T2DM compared with those without T2DM[101].

Diabetes mellitus and liver disease

Nonalcoholic fatty liver disease

The consequences of nonalcoholic fatty liver disease (NAFLD) make it important to recognize the burden of this disease among people with diabetes mellitus. NAFLD and nonalcoholic steatohepatitis (NASH; an advanced form of NAFLD) are major causes of liver transplantation in the general population. In the USA, NASH accounted for 19% of liver transplantations in 2016 — second only to alcoholic liver disease, which was the cause of 24% of transplantations[102]. In Australia and New Zealand, NAFLD was the primary diagnosis in 9% of liver transplant recipients in 2019, only slightly below the figure for alcoholic cirrhosis of 13%[103]. In Europe, NASH increased as the reason for transplantations from 1% in 2002 to more than 8% in 2016, in parallel with the rising prevalence of diabetes mellitus[104].

NAFLD is highly prevalent among people with T2DM. In a systematic review of 80 studies across 20 countries/regions, the prevalence of NAFLD among 49,419 people with T2DM was 56%[105], while the global prevalence of NAFLD in the general population is estimated to be 25%[106]. In a Chinese cohort study of 512,891 adults, diabetes mellitus was associated with an adjusted HR of 1.76 (95% CI 1.47–2.16) for NAFLD compared with no diabetes mellitus[107] (TABLE 3). Another smaller longitudinal Chinese study also reported an increased risk of developing NAFLD among those with T2DM compared with those without T2DM[108]. However, most evidence regarding the association between NAFLD and diabetes mellitus is from cross-sectional studies[109–111].

NASH and fibrosis

Diabetes mellitus appears to enhance the risk of NAFLD complications, including NASH and fibrosis. An analysis of 892 people with NAFLD and T2DM across 10 studies showed that the prevalence of NASH was 37% (REF.[105]); figures for the prevalence of NASH in the general

Table 3 | **Summary of original studies reporting risk of liver disease associated with diabetes mellitus**

Study	Diabetes mellitus type	Study type included (*n*)	Outcome	Risk associated with diabetes mellitus (95% confidence interval)
Pang et al. (2018)[107]	All	Cohort (512,891)	NAFLD	HR 1.76 (1.47–2.16)
Li et al. (2017)[108]	T2DM	Cohort (18,111)	NAFLD	OR 1.40 (1.22–1.62)
Loomba et al. (2012)[113]	All	Cross-sectional (1,069)	NASH	OR 1.93 (1.37–2.73)
			Liver fibrosis	OR 3.31 (2.26–4.85)

HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; T2DM, type 2 diabetes mellitus.

population with NAFLD vary greatly across different study populations, ranging from 16% to 68%[112]. Amongst 439 people with T2DM and NAFLD in seven studies, 17% had advanced fibrosis[105]. An analysis of 1,069 people with NAFLD in a US study found that diabetes mellitus was an independent predictor for NASH (OR 1.93, 95% CI 1.37–2.73) and fibrosis (3.31, 95% CI 2.26–4.85)[113].

Bidirectional relationship between diabetes mellitus and liver disease. The relationship between diabetes mellitus and NAFLD is bidirectional, as NAFLD is associated with an increased risk of developing T2DM[114]. There is also a notable bidirectional relationship between diabetes mellitus and liver cirrhosis. The prevalence of diabetes mellitus in people with liver cirrhosis has been reported as 20–63%, depending on the severity of liver damage, aetiology and diagnostic criteria[115]. In an Italian study of 401 participants with cirrhosis, 63% of those with decompensated liver disease had diabetes mellitus compared with 10% of those with well-compensated liver disease[116], suggesting that diabetes mellitus is more common in severe cases of liver damage. The association between diabetes mellitus and cirrhosis also varies according to the cause of liver disease. In a US study of 204 people with cirrhosis, the prevalence of diabetes mellitus was 25% among those with cirrhosis caused by hepatitis C virus, 19% among those with cirrhosis from alcoholic liver disease and only 1% among those with cirrhosis due to cholestatic liver disease[117]. Among the causes of cirrhosis, haemochromatosis has the strongest association with diabetes mellitus, with diabetes mellitus mainly resulting from the iron deposition that is characteristic of haemochromatosis[118].

Potential aetiological mechanisms

Several factors have been implicated in the aetiology of liver disease in people with diabetes mellitus, with insulin resistance being the most notable[119].

Insulin resistance. Insulin resistance causes lipolysis, thereby increasing the circulating levels of free fatty acids, which are then taken up by the liver as an energy source[120]. These fatty acids overload the mitochondrial β-oxidation system in the liver, resulting in the accumulation of fatty acids and, consequently, NAFLD[121]. Of those individuals with NAFLD, 2–3% develop hepatic inflammation, necrosis and fibrosis, which are the hallmarks of NASH[122]. The exact mechanisms leading to steatohepatitis are unclear, although dysregulated peripheral lipid metabolism appears to be important[14].

Ectopic adipose deposition. Excessive or ectopic deposition of adipose tissue around the viscera and in the liver might be an important mechanism underlying both T2DM and liver disease, particularly NAFLD[123]. Dysfunction of long-term adipose storage in white adipose tissue is known to lead to ectopic adipose deposition in the liver. In this state, increased levels of fatty acyl-coenzyme As, the activated form of fatty acids, might lead to organ dysfunction, including NAFLD[124]. Ectopic adipose deposition leading to organ-specific insulin resistance has emerged as a major hypothesis for the pathophysiological basis of T2DM, and ectopic adipose in the pancreas could contribute to β-cell dysfunction and, thus, the development of T2DM[125].

Diabetes mellitus and affective disorders

Depression

The prevalence of depression appears to be high among people with diabetes mellitus. The strongest evidence for an association comes from a systematic review of 147 studies among people with T2DM, which revealed a mean prevalence of depression of 28%[126], while the global prevalence of depression in the general population is estimated at around 13%[127]. For T1DM, a systematic review reported a pooled prevalence of depression of 12% compared with only 3% in those without T1DM[128]. The risk of depression among people with diabetes mellitus appears to be roughly 25% greater than the risk in the general population, with consistent findings across several meta-analyses (TABLE 4). A 2013 study found an adjusted RR of 1.25 (95% CI 1.10–1.44) for incident depression among people with diabetes mellitus compared with those without diabetes mellitus[129]. Another systematic review of people with T2DM reported a near identical effect size[130].

Anxiety and eating disorders

Evidence exists for an association of diabetes mellitus with anxiety, and of T1DM with eating disorders. In a systematic review involving 2,584 individuals with diabetes mellitus, a prevalence of 14% was found for generalized anxiety disorder and 40% for anxiety symptoms, whereas the prevalence of generalized anxiety disorder in the general population is estimated as only 3–4%[131]. People with diabetes mellitus had an increased risk of anxiety disorders (OR 1.20, 95% CI 1.10–1.31) and anxiety symptoms (OR 1.48, 95% CI 1.02–1.93) compared with those without diabetes mellitus in a meta-analysis[132] (TABLE 4), although these findings were based on cross-sectional data. Across 13 studies, 7% of adolescents with T1DM

were found to have eating disorders, compared with 3% of peers without diabetes mellitus[133].

Broader psychological impacts

There is a substantial literature on a broad range of psychological impacts of diabetes mellitus. Social stigma[134] can have profound impacts on the quality of life of not only people with diabetes mellitus, but their families and carers, too[135]. In a systematic review, diabetes mellitus distress was found to affect around one-third of adolescents with T1DM, which was consistent with the results of studies of adults with diabetes mellitus[136]. Diabetes mellitus burnout appears to be a distinct concept, and is characterized by exhaustion and detachment, accompanied by the experience of a loss of control over diabetes mellitus[137].

Potential aetiological mechanisms

Diabetes mellitus and depression appear to have common biological origins. Activation of the innate immune system and acute-phase inflammation contribute to the pathogenesis of T2DM — increased levels of inflammatory cytokines predict the onset of T2DM[138] — and there is growing evidence implicating cytokine-mediated inflammation in people with depression in the absence of diabetes mellitus[139]. Dysregulation of the hypothalamic–pituitary–adrenal axis is another potential biological mechanism linking depression and diabetes mellitus[140]. There have been numerous reports of hippocampal atrophy, which might contribute to chronic activation of the hypothalamic–pituitary–adrenal axis, in individuals with T2DM as well as those with depression[141,142]. A meta-analysis found that, although hypertension modified global cerebral atrophy in those with T2DM, it had no effect on hippocampal atrophy[143]. This suggests that, although global cerebral atrophy in individuals with T2DM might be driven by atherosclerotic disease, hippocampal atrophy is an independent effect that provides a common neuropathological aetiology for the comorbidity of T2DM with depression. There is a lack of relevant information regarding the potential aetiological mechanisms that link diabetes to other affective disorders.

Diabetes mellitus and sleep disturbance

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is highly prevalent among people with diabetes mellitus. In a systematic review of 41 studies of adults with diabetes mellitus, the prevalence of OSA was found to be 60%[144], whereas reports for OSA prevalence in the general population range from 9% to 38%[145]. In a UK study of 1,656,739 participants, T2DM was associated with an IRR for OSA of 1.48 (95% CI 1.42–1.55) compared with no T2DM[146]. A population-based US study reported a HR of 1.53

Table 4 | **Summary of major systematic reviews reporting risk of affective disorders, cognitive disability and functional disability associated with diabetes mellitus**

Author	Diabetes mellitus type	Study type included (*n*)	Outcome	Risk associated with diabetes mellitus (95% confidence interval)
Rotella et al. (2013)[129]	All	Cohort, cross-sectional (497,223)	Depression	HR 1.25 (1.10–1.44)
Nouwen et al. (2019)[194]	T2DM	Cohort, cross-sectional (48,808)	Depression	RR 1.24 (1.09–1.40)
Smith et al. (2013)[132]	All	Cohort, cross-sectional (12,626)	Anxiety disorders	OR 1.20 (1.10–1.31)
			Anxiety symptoms	OR 1.48 (1.02–1.93)
Lu et al. (2009)[154]	All	Cohort (23,257)	Vascular dementia	RR 2.38 (1.79–3.18)
			Alzheimer disease	RR 1.39 (1.16–1.66)
Cheng et al. (2012)[155]	All	Cohort (44,714)	Vascular dementia	RR 2.48 (2.08–2.96)
			Alzheimer disease	RR 1.46 (1.20–1.77)
			All-cause dementia	RR 1.51 (1.31–1.74)
			MCI	RR 1.21 (1.02–1.45)
Li et al. (2019)[156]	All	Cohort (1,257,144[a])	All-cause dementia	RR 1.69 (1.38–2.07)
Xue et al. (2019)[157]	All	Cohort, cross-sectional (4,349,111)	All-cause dementia	RR 1.43 (1.33–1.53)
Pal et al. (2018)[158]	T2DM	Cohort (6,865)	Progression to dementia in MCI	OR 1.53 (1.20–1.97)
Wong et al. (2013)[173]	All	Cohort, cross-sectional (162,534[a])	Mobility disability	OR 1.51 (1.38–1.64)
			ADL disability	OR 1.82 (1.40–2.36)
			IADL disability	OR 1.65 (1.55–1.74)
Yang et al. (2016)[172]	All age ≥60 years	Cohort (14,685)	Falls	RR 1.64 (1.27–2.11)

ADL, activities of daily living; HR, hazard ratio; IADL, independent activities of daily living; MCI, mild cognitive impairment; OR, odds ratio; RR, relative risk. [a]Total number of participants obtained through sum of individual study cohort sizes listed in tables or otherwise.

(95% CI 1.32–1.77) for OSA in people with T2DM compared with those without diabetes mellitus[147]. However, the association in this latter report was attenuated after adjustment for BMI and waist circumference (1.08, 95% CI 1.00–1.16), suggesting that the excess risk of OSA among people with diabetes mellitus might be mainly explained by the comorbidity of obesity. Although most studies on OSA have focused on T2DM, a meta-analysis of people with T1DM revealed a similar prevalence of 52%[148]; however, this meta-analysis was limited to small studies. The association between T2DM and OSA is bidirectional: the severity of OSA was shown to be positively associated with the incidence of T2DM, independent of adiposity, in a large US cohort study[149].

Potential aetiological mechanisms

The mechanism by which T2DM might increase the risk of developing OSA is thought to involve dysregulation of the autonomic nervous system leading to sleep-disordered breathing[150]. Conversely, the specific mechanism behind OSA as a causative factor for T2DM remains poorly understood. It has been suggested that OSA is able to induce insulin resistance[151,152] and is a risk factor for the development of glucose intolerance[152]. However, once T2DM has developed, there is no clear evidence that OSA worsens glycaemic control, as an RCT of people with T2DM found that treating OSA had no effect on glycaemic control[153].

Diabetes mellitus and cognitive disability

Dementia and cognitive impairment

Dementia is emerging as a major cause of mortality in both individuals with diabetes mellitus and the general population, and is now the leading cause of death in some countries/regions[9]. However, compared with the general population, diabetes mellitus increases the risk of dementia, particularly vascular dementia. The association is supported by several systematic reviews, including one of eight population-based studies with more than 23,000 people, which found SRRs of 2.38 (95% CI 1.79–3.18) for vascular dementia and 1.39 (95% CI 1.16–1.66) for Alzheimer disease comparing people with diabetes mellitus with those without diabetes mellitus[154] (TABLE 4). Similar results, as well as a RR of 1.21 (95% CI 1.02–1.45) for mild cognitive impairment (MCI), were reported across 19 population-based studies of 44,714 people, 6,184 of whom had diabetes mellitus[155]. Two meta-analyses of prospective cohort studies have shown increased risks of all-cause dementia in people with diabetes mellitus compared with those without diabetes mellitus[156,157], and T2DM has been shown to increase progression to dementia in people with MCI[158].

The boundaries between Alzheimer disease and vascular dementia remain controversial, and these conditions are often difficult to differentiate clinically[159]. Consequently, vascular dementia might have been misdiagnosed as Alzheimer disease in some studies investigating diabetes mellitus and dementia, resulting in an overestimation of the effect size of the association between diabetes mellitus and Alzheimer disease. Although a cohort study found a significant association between diabetes mellitus and Alzheimer disease using imaging[160], autopsy studies have failed to uncover an association between diabetes mellitus and Alzheimer disease pathology[161,162], suggesting that vascular mechanisms are the key driver of cognitive decline in people with diabetes mellitus.

Another important finding is a 45% prevalence of MCI among people with T2DM in a meta-analysis, compared with a prevalence of 3–22% reported for the general population[163]. Notably, however, the prevalence of MCI in individuals with T2DM was similar in people younger than 60 years (46%) and those older than 60 years (44%), which is at odds with previous research suggesting that MCI is most common in older people, particularly those aged more than 65 years[164] However, another meta-analysis found cognitive decline in people with T2DM who are younger than 65 years[165], suggesting that a burden of cognitive disease exists among younger people with diabetes mellitus.

Potential aetiological mechanisms

Although there is solid evidence that links diabetes mellitus to cognitive disability, our understanding of the underlying mechanisms is incomplete. Mouse models suggest a strong association between hyperglycaemia, the advanced glycation end products glyoxal and methylglyoxal, enhanced blood–brain barrier (BBB) permeability and cognitive dysfunction in both T1DM and T2DM[166]. The BBB reduces the access of neurotoxic compounds and pathogens to the brain and sustains brain homeostasis, so disruption to the BBB can result in cognitive dysfunction through dysregulation of transport of molecules between the peripheral circulation and the brain[167]. There appears to be a continuous relationship between glycaemia and cognition, with associations found between even high-normal blood levels of glucose and cognitive decline[168]. Another hypothetical mechanism involves a key role for impaired insulin signalling in the pathogenesis of Alzheimer disease. Brain tissue obtained post mortem from individuals with Alzheimer disease showed extensive abnormalities in insulin and insulin-like growth factor signalling mechanisms compared with control brain tissue[169]. Although the synthesis of insulin-like growth factors occurred normally in people with Alzheimer disease, their expression levels were markedly reduced, which led to the subsequent proposal of the term 'type 3 diabetes' to characterize Alzheimer disease.

Diabetes mellitus and disability

Functional disability

Disability (defined as a difficulty in functioning in one or more life domains as experienced by an individual with a health condition in interaction with contextual factors)[170] is highly prevalent in people with diabetes mellitus. In a systematic review, lower-body functional limitation was found to be the most prevalent disability (47–84%) among people with diabetes mellitus[171] The prevalence of difficulties with activities of daily living among people with diabetes mellitus ranged from 12% to 55%, although most studies were conducted exclusively in individuals aged 60 years and above, so the results are not generalizable to younger age groups. A systematic

Activities of daily living
Fundamental skills required to independently care for oneself such as eating, bathing and mobility.

Independent activities of daily living
Activities that allow an individual to live independently in a community.

Immortal time bias
The error in estimating the association between an exposure and an outcome that results from misclassification or exclusion of time intervals.

review showed a significant association between diabetes mellitus and falls in adults aged 60 years and above[172]. A 2013 meta-analysis[173] showed an increased risk of mobility disability, activities of daily living disability and independent activities of daily living disability among people with diabetes mellitus compared with those without diabetes mellitus (TABLE 4). Although this analysis included cross-sectional data, results were consistent across longitudinal and cross-sectional studies, suggesting little effect of reverse causality. However, people with functional disabilities that limit mobility (for example, people with osteoarthritis or who have had a stroke) might be more prone to developing diabetes mellitus owing to physical inactivity[174].

Workplace productivity. Decreased productivity while at work, increased time off work and early dropout from the workforce[175] are all associated with diabetes mellitus, probably partly due to functional disability, and possibly also to comorbidities such as obesity and physical inactivity[176]. Given that young-onset diabetes is becoming more common, and most people with diabetes mellitus in middle-income countries/regions are less than 65 years old[177], a pandemic of diabetes mellitus-related work disability among a middle-aged population does not bode well for the economies of these regions.

Potential aetiological mechanisms

The mechanisms by which diabetes mellitus leads to functional disability remain unclear. One suggestion is that hyperglycaemia leads to systemic inflammation, which is one component of a multifactorial process that results in disability[154]. The rapid loss of skeletal muscle strength and quality seen among people with diabetes mellitus might be another cause of functional disability[178] (BOX 1). In addition, complications of diabetes mellitus, including stroke, peripheral neuropathy and cardiac dysfunction, can obviously directly cause disability[179].

Diabetes management and control

Although a detailed discussion of the impacts of anti-diabetes mellitus medications and glucose control on emerging complications is beyond the scope of this Review, their potential effect on these complications must be acknowledged.

Box 1 | **Diabetes mellitus and skeletal muscle atrophy**

- Individuals with diabetes mellitus exhibit skeletal muscle atrophy that is typically mild in middle age and becomes more substantial with increasing age.
- This muscle loss leads to reduced strength and functional capacity and, ultimately, increased mortality.
- Skeletal muscle atrophy results from a negative balance between the rate of synthesis and degradation of contractile proteins, which occurs in response to disuse, ageing and chronic diseases such as diabetes mellitus.
- Degradation of muscle proteins is more rapid in diabetes mellitus, and muscle protein synthesis has also been reported to be decreased.
- Proposed mechanisms underlying skeletal muscle atrophy include systemic inflammation (affecting both protein synthesis and degradation), dysregulation of muscle protein anabolism and lipotoxicity.
- Mouse models have also revealed a key role for the WWP1/KLF15 pathway, mediated by hyperglycaemia, in the pathogenesis of muscle atrophy.

See REFS[195–198].

Medications

Anti-diabetes mellitus medications and cancer. In the case of cancer as an emerging complication, the use of medications for diabetes mellitus was not controlled for in most studies of diabetes mellitus and cancer and might therefore be a confounding factor. People taking metformin have a lower cancer risk than those not taking metformin[180]. However, this association is mainly accounted for by other factors. For example, metformin is less likely to be administered to people with diabetes mellitus who have kidney disease[181], who typically have longer duration diabetes mellitus, which increases cancer risk. A review of observational studies into the association between metformin and cancer found that many studies reporting significant reductions in cancer incidence or mortality associated with metformin were affected by immortal time bias and other time-related biases, casting doubt on the ability of metformin to reduce cancer mortality[182]. Notably, the use of insulin was associated with an increased risk of several cancers in a meta-analysis[183]. However, in an RCT of more than 12,000 people with dysglycaemia, randomization to insulin glargine (compared with standard care) did not increase cancer incidence[184]. Furthermore, cancer rates in people with T1DM and T2DM do not appear to vary greatly, despite substantial differences in insulin use between people with these types of diabetes mellitus.

Anti-diabetes mellitus medications and other emerging complications. Anti-diabetes medications appear to affect the onset and development of some other emerging complications of diabetes mellitus. Results from RCTs suggest that metformin might confer therapeutic effects against depression[185], and its use was associated with reduced dementia incidence in a systematic review[186]. In an RCT investigating a potential association between metformin and NAFLD, no improvement in NAFLD histology was found among people using metformin compared with those given placebo[187]. An RCT reported benefits of treatment with the glucagon-like peptide 1 receptor agonist dulaglutide on cognitive function in a post hoc analysis[188], suggesting that trials designed specifically to test the effects of dulaglutide on cognitive function should be undertaken.

Glucose control

Another important consideration is glycaemic control, which appears to have variable effects on emerging complications. A meta-analysis found no association of glycaemic control with cancer risk among those with diabetes mellitus[189], and an RCT found no effect of intensive glucose lowering on cognitive function in people with T2DM[190]. However, glycaemic control has been associated with improved physical function[191], decreased COVID-19 mortality[192] and a decreased risk of NAFLD[193] in observational studies of patients with diabetes mellitus; notably, no RCTs have yet confirmed these associations.

Conclusions

With advances in the management of diabetes mellitus and associated increased life expectancy, the face of diabetes mellitus complications is changing. As the management of glycaemia and traditional complications of diabetes mellitus is optimized, we are beginning instead to see deleterious effects of diabetes mellitus on the liver, brain and other organs. Given the substantial burden and risk of these emerging complications, future clinical and public health strategies should be updated accordingly. There is a need to increase the awareness of emerging complications among primary care physicians at the frontline of diabetes mellitus care, and a place for screening for conditions such as depression, liver disease and cancers in diabetes mellitus guidelines should be considered. Clinical care for older people with diabetes mellitus should target physical activity, particularly strength-based activity, to reduce the risk of functional disability in ageing populations. Ongoing high-quality surveillance of diabetes mellitus outcomes is imperative to ensure we know where the main burdens lie. Given the growing burden of these emerging complications, the traditional management of diabetes mellitus might need to broaden its horizons.

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