Alcohol and illicit drug use in people with diabetes

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As the prevalence of type 1 and type 2 diabetes increases and population-level patterns of alcohol and illicit drug use evolve, clinicians will continue to encounter people with diabetes whose substance use is affecting health outcomes. Substance use contributes substantially to the population-level prevalence of cardiovascular events, cerebrovascular events, cancers, mental health conditions, road trauma, and domestic violence. Alcohol and drug use also have a measurable effect on diabetes incidence and the development of both acute and chronic diabetes-related complications. In this Review, we examine the effect of alcohol and illicit drug use on people with type 1 or type 2 diabetes. We describe evidence for substance use as a risk factor for new-onset diabetes, prevalence of use in people with diabetes, evidence linking substance use with diabetes-related health outcomes, and evidence on the management of these co-occurring conditions.

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Introduction

People with diabetes who consume alcohol and illicit drugs are reported throughout the health system. The use of substances in the highly prevalent population of people with diabetes creates difficulties with the meeting of blood glucose targets and the subsequent acute and chronic complications of diabetes. Diabetes has a worldwide prevalence of 8·8%, with an estimated 451 million people affected. By 2045, more than 600 million people globally are estimated to be living with diabetes.[1] Complications of diabetes, including cardiovascular, cerebrovascular, renal, and neurological outcomes, have contributed to 4 million deaths globally in 2017, and accounted for 10·7% of all-cause mortality.[1]

Like diabetes, the harm from excess alcohol use is multifactorial. Alcohol contributes substantially to hepatic and neurological disease, different cancers (liver, head and neck, breast, and gastrointestinal), road trauma, domestic violence, and other mental health disorders, including suicide.[2] Estimates suggest that alcohol consumption causes 2·2% of female and 6·8% of male deaths globally, making it the seventh leading cause of both mortality and disability-adjusted life-years.[2] Alcohol use disorders are also the most prevalent substance use disorder with an estimated 100·4 million diagnoses worldwide.[3]

Prevalence of illicit drug use in the general community is changing rapidly. Cannabis has been legalised in multiple jurisdictions and the use of other previously stigmatised substances, such as cocaine and other stimulants, has become more acceptable. However, the harmful effects of cannabis include an earlier onset and poorer trajectory of psychotic and other mental health conditions, cognitive effects, cannabis hyperemesis syndrome, and respiratory conditions. Stimulants are associated with early-onset cardiac and cerebrovascular events, and malignant hyperthermia and hyponatraemia in overdose.[3] Furthermore, the mostly iatrogenic exposure of the population to increasing doses of opioids for chronic pain has contributed to an opioid use disorder. Deaths from opioid drug overdoses account for more than 50 000 per year in the USA alone.[3,4] Intravenous use of any illicit drug is associated with injection site infections, bacterial endocarditis, and blood-borne virus transmission, of which HIV, hepatitis B, and hepatitis C are most common. Worldwide estimates suggest that 22·1 million people have a cannabis use disorder and 26·8 million people have an opioid use disorder.[3] Data from the National Epidemiologic Survey on alcohol and related conditions in the USA reported a 9·9% estimate of a lifetime Diagnostic and Statistical Manual of Mental Disorders 5 drug use disorder.[5] Thus, both substance use and diabetes are substantial contributors to worldwide premature mortality and the global burden of disease. Their prevalence is both regionally and socioeconomically established. Both substance use and diabetes, at least for type 2 diabetes, are mostly preventable risk factors for a wide array of acute and chronic multiorgan conditions across the lifespan.[6,7]

It is important to understand the effects of different drug classes on the development and natural history of diabetes. However, because of the paucity of controlled experimental data, reliance on secondary analyses of medical registers or other datasets, along with the long delays between substance use and diabetes-related outcomes, establishing causality between particular substances and outcomes is difficult. Despite the research limitations, there is a recognition that prevention of both substance use and diabetes are opportunities for substantive health gains.[4,6,7] Thus, current research leveraging the most effective clinical and public health strategies is helping to manage this important diabetes comorbidity.[7]

In this Review, we examine the evidence for the effect of alcohol and recreational drug use on individuals with type 1 or type 2 diabetes. We discuss alcohol and drug use as risk factors for diabetes, the prevalence of substance use and substance use disorders in people with diabetes, the effect of alcohol and drug use on acute and chronic complications, and the management of these commonly co-occurring conditions (panel 1). We distinguish between any quantity of substance use and use associated with a substance use disorder where individuals have impaired control, prioritise alcohol or drug consumption, experience harm and functional decline, and exhibit physiological aspects such as tolerance and withdrawal (panel 3). Tobacco use (and other nicotine-delivery devices, such as electronic cigarettes) and other forms of diabetes,

Panel 1: **Fictional case vignettes**

Case 1

A 26-year-old woman with type 1 diabetes (diagnosed at 2 years old) presented for her regular outpatient review. She works in advertising and lives with her housemate in rented accommodation. Upon presentation, she took basal bolus insulin (15 units insulin glargine daily and 4–8 units insulin aspart before every meal). Her most recent HbA_{1c} was 69·4 mmol/mol (8·5%). She had non-proliferative diabetic retinopathy but no nephropathy or macrovascular complications. She described an episode of hypoglycaemia 3 weeks before her review, with a measured blood glucose of 1·8 mmol/L. On further questioning, this episode occurred at 0400 h when she collapsed in the bathroom of a local nightclub with little warning. She had consumed one pill of 3, 4-methylenedioxymethamphetamine (ecstasy) and one and a half bottles of wine commencing at 2300 h the evening before. She commented that she presumed most of the people around her thought she was "just drunk", but her friend recognised "what was going on" and gave her some soft drink to which she slowly responded. She further said, "I have no idea how she picked I was having a hypo". She had not reported this episode to any of her clinicians before this consult.

After we reviewed her diabetes management more generally, we screened for alcohol and other drug use disorders and did a short counselling session entailing non-judgmental feedback on the potential risks of alcohol and drug use. We discussed harm reduction measures (panel 2) that she could put in place to reduce the future risk of hypoglycaemia.

Case 2

A 67-year-old retired construction worker with type 2 diabetes was admitted to hospital with an infected lower limb ulcer. He lives with his wife in his own home, and was diagnosed with diabetes by his family physician 18 months before being admitted to hospital, through a screening of fasting blood glucose concentrations. His most recent HbA_{1c} was 66·1 mmol/mol (8·2%) and he had never checked his blood glucose concentrations at home. His diabetes was being managed through his family physician and he visited the clinic nurse and his doctor every 3 months. Since his diagnosis, he has been walking for 45 mins daily and replaced his lunch with either a salad or soup; however, he has not yet lost weight. Upon presentation, his medication was a combination of 1000 mg metformin extended release and 100 mg sitagliptin, 150 mg irbesartan, 10 mg rosuvastatin, and 100 mg aspirin, and he reported taking his medications regularly. His BMI is 31 kg/m^2, blood pressure 155/90 mm Hg, and blood glucose concentrations on the ward have been between 8 mmol/L and 14 mmol/L. He quit smoking tobacco 15 years ago. After direct questioning, he reported drinking six 330 mL bottles of full-strength beer daily for the past 15 years, which "may have increased a little since I retired." He reported that his father had an alcohol use disorder and noted that there might have been times in the past where he found alcohol intake difficult to control, but felt that "it's not too much of a problem."

After we reviewed his diabetes management more generally, we screened him for an alcohol and drug use disorder and found that he fit the criteria for an alcohol use disorder. After some motivational interviewing, he acknowledged the harm of his ongoing drinking and the importance of an initial period of abstinence from alcohol. Although he declined a referral to a specialist service, we encouraged him to engage in counselling, peer-led support groups, and prescribed him naltrexone, in addition to his regular regimen.

such as gestational diabetes and diabetes secondary to pancreatic insufficiency, are not discussed in this Review.

Substance use as a risk factor for development of diabetes

There is no evidence that alcohol or drug use leads to the development of type 1 diabetes, which has a peak incidence below the age of 14 years, generally before the onset of substantial substance use.[10] By contrast, large observational datasets show an association between alcohol and recreational drugs with the incidence of type 2 diabetes.[11,12]

As with cardiovascular disease,[13] the relationship between alcohol and the development of type 2 diabetes follows a U-shaped relationship, in which the lowest risk of a future diagnosis of diabetes occurs at moderate levels (5–20 g per day) of consumption. This relationship has been replicated in large, prospective, epidemiological studies and twin studies, which have shown that consumption rates of 5–20 g of alcohol a day are associated with a reduced risk of developing diabetes.[11,12,14] Some studies have suggested that beverage type might influence the association, with wine (as opposed to spirits or beer) being linked to an apparent reduction in diabetes incidence.[15,16] Proposed physiological mechanisms for these observed effects of alcohol include an anti-inflammatory effect, an increase in insulin sensitivity, and a rise in adiponectin concentrations linked to weight gain.[17,18] At higher doses, harmful effects of alcohol include hypertriglyceridaemia, hypertension, and both decreased insulin secretion and increased insulin resistance.[19,20]

The size and validity of the U-shaped relationship between alcohol and cardiovascular disease more broadly, and diabetes in particular, have been questioned.[13] Potential weaknesses in the design and interpretation of studies include the influence of so-called sick quitters where abstainers might have ceased drinking for health reasons. Other important confounders known to be risk factors for type 2 diabetes include high intake of energy dense foods, fatty liver disease, polysubstance use, psychiatric morbidities, and reduced exercise.[21] Analyses that used inherited differences in alcohol metabolism for mendelian randomisation suggest that most of the previously asserted protective effects were likely due to unmeasured confounding factors. These studies show that any protective effects of alcohol are probably restricted to non-Asian women.[12,22,23]

The relationship between the use of cannabis and opioids and the onset of diabetes has been reported in the published literature. Despite the appetite-stimulating effect of cannabis and its propensity to increase consumption of low nutritional value carbohydrates, cross-sectional datasets have consistently found that people who report cannabis use have a modestly lower prevalence of both obesity and diabetes than matched controls.[24,25] Although this finding has led to speculation about a direct metabolic effect of cannabinoids, no dose-response effect has been shown and confounders, such as a well smoker effect (where people who are unwell have quit or cannot tolerate cannabis), recall bias, and relatively low cannabis exposure in these surveys might be more likely explanations. By contrast, a study of the metabolic profile of 30 healthy and heavy cannabis users (median age of 27 years) with a self-reported history of 9 years of daily use, showed increased abdominal fat in cannabis

Panel 2: Harm reduction strategies specific for diabetes

For all substances

- Look up the effects of the substance on diabetes or discuss them with a health professional
- Keep count of the amount of substance consumed
- Wear a medical alert identification bracelet
- Always use with companions who are aware of the diabetes
- Avoid consuming substances to intoxication
- Avoid mixing substances
- Increase the frequency of blood glucose measurements
- Do not omit insulin
- Snack regularly
- Carry extra short-acting carbohydrates
- Discuss alcohol and drug use with a health professional
- For stimulants (and possibly cannabis), be aware of the risk of hyperglycaemia and ketoacidosis

For alcohol

- Be aware of the risk of nocturnal hypoglycaemia, especially if on insulin or insulin secretagogues
- Eat carbohydrate-rich foods before and after drinking
- Reduce long-acting insulin dose or use a temporary basal rate if using an insulin pump

Panel 3: Definitions of substance use disorder

Diagnostic and Statistical Manual of Mental Disorders-5 criteria for substance use disorder (two to three mild, four to five moderate, six or more severe, in a given year)[8]

- Using more than planned or for a longer interval than desired
- Inability to cut down despite desire to do so
- Spending a substantial amount of the day obtaining, using, or recovering from substance use
- Craving or intense urges to use
- Repeated use results in an inability to meet important social or professional obligations
- Persistent use despite problems caused at work, school, or home
- Cutting back on important social, professional, or leisure activities because of use
- Using in physical hazardous situations
- Persistent use despite awareness that use is causing or worsening a physical or mental problem
- Tolerance: needing an increasing amount to achieve the desired effects
- Withdrawal: characteristic group of physical effects or symptoms emerge as substance level drops

International Classification of Disorders-10 dependence syndrome (three or more present in a given year)[9]

- A strong desire or sense of compulsion to take the substance
- Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use
- A physiological withdrawal state when substance use has been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same substance (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms
- Evidence of tolerance, such that increased doses of the psychoactive substances are required to achieve effects originally produced by lower doses
- Progressive neglect of alternative pleasures or interests because of psychoactive substance use, and increased amount of time necessary to obtain or take the substance or to recover from its effects
- Persisting with substance use despite clear evidence of overtly harmful consequences

users not associated with an effect on lipid or glucose metabolism.[26] The longitudinal prospective Coronary Artery Risk Development in Young Adults study[27] found an increased risk of prediabetes (odds ratio [OR] 1·65, 95% CI 1·15–2·38) over a 25-year period in 3034 individuals (43–55 years). A Swedish prospective study of 18 000 participants showed no change in the incidence of diabetes in cannabis smokers versus non-smokers once adjusted for age.[28]

Despite previous studies showing a propensity of opioids to cause hyperglycaemia, a case-control study of 50 468 individuals with a new diagnosis of type 2 diabetes showed no association with opioid prescribing in the previous 2 years when controlled for the risk factors of BMI, smoking, and antihypertensives.[29] There is no available epidemiological evidence exploring an association between stimulants or other illicit drug classes and the onset of diabetes.

Prevalence of substance use in people with diabetes

Few population-based surveys are available that explore patterns of substance use in either type 1 or type 2 diabetes populations. Although the available data indicate a reduced prevalence of overall alcohol and substance use, there is no reduction in the diagnosis of substance use disorders in those with diabetes compared with controls. In both type 1 and type 2 diabetes, this finding might reflect a reduction of substance use as part of chronic disease management in some groups, but a worsening of substance use patterns in others, possibly in those with diabetes distress and depression.

Type 1 diabetes

Surveys of adolescents (15–18 years) and young adults (18–25 years) with type 1 diabetes typically reveal that they report consuming alcohol and illicit substances at similar or slightly lower amounts than controls.[30,31] A study of 164 adolescents with type 1 diabetes in Alberta, Canada indicated that they had reported consuming

alcohol (51·8%), tobacco (27·4%), or cannabis (22·6%) in their lifetime.[31] This result matched a survey of the general population with the exception of a marked difference in the prevalence of other illicit substance use, which ranged from 36% in the general population to 7·3% in those with type 1 diabetes.[31] However, on reaching young adulthood (18–25 years), substance use patterns of people with type 1 diabetes were more similar to those of the general population.[32,33]

Type 2 diabetes

The largest surveys on alcohol consumption show a reduced use in people diagnosed with type 2 diabetes relative to matched controls.[34,35] In 2010, data from the US National Alcohol Survey showed that of 5240 people, 12·1% developed type 2 diabetes over a 10-year period. Those with a new diagnosis were more likely to report having subsequently reduced heavy drinking (OR 1·7, 95% CI 1·1–2·6) than those who had not developed type 2 diabetes.[35] This reduction is associated with improved diabetes-related health behaviours.[36] However, the reduction in consumption is not matched by a reduction in alcohol use disorders. In a large analysis of electronic medical records for 16 243 (4·0%) people with type 2 diabetes, there was an increased prevalence of alcohol use disorders compared with the general population (2·3%).[37] An explanation for this finding might be that as people with type 2 diabetes reduce their alcohol intake, those with an alcohol use disorder remain over-represented because of an increased incidence.

Regarding drug use disorders, the same study showed an increased prevalence of use in people with type 2 diabetes (4·2%) compared with the general population (2·1%).[37] This subgroup of people with substance use disorders and diabetes go on to have considerably worse outcomes than those with only diabetes. Another study assessed 10% of individuals from a large North American health service who were most likely admitted to hospital for diabetes-related complications. They found that in these individuals, the frequency of substance use disorders approached 50%.[38]

Notably, an important subgroup of patients with an increased risk of substance use disorders are individuals with obesity who have had bariatric surgery. This cohort has a 9% increase in alcohol use disorders 2–7 years after gastric bypass surgery compared with before surgery; however, this increase was not found for those who had laparoscopic adjustable gastric banding.[39] This finding might be partly explained by effective higher exposures to alcohol through altered postoperative absorption, resulting in higher peak alcohol concentrations.[40] Altered ghrelin concentrations in appetite and reward processing in the hypothalamus and striatum have also been postulated to result in an alcohol for food substitution effect.[40]

People with type 2 diabetes tend to have higher rates of treatment with opioids than do the general population. Management of painful conditions associated with diabetes, such as diabetic peripheral neuropathy, can result in opioid overprescribing and opioid use disorders.[41] Notably, type 2 diabetes is a risk factor for ongoing use of postoperative opioid analgesia at 90 days (OR 1·27, 95% CI 1·12–1·44).[42] For bariatric surgery, relative to medical treatments, the absolute risk increase of postoperative opioid use disorder is 3·6%.[43]

The scarce data available regarding the prevalence of diabetes in people referred for addiction treatment show an over-representation relative to the general population. A meta-analysis of seven cross-sectional studies, including 3998 people with alcohol use disorders, found a prevalence of diabetes of 9·9% in the general population and 17·2% prevalence in the treatment-seeking population.[44] In two US groups, one consisting of women with risk factors for HIV and using an opioid agonist treatment, and another of individuals receiving opioid agonist therapy, the prevalence of diabetes was between 15% and 25%.[45,46]

Substance use and its effect on diabetes outcomes

Advances in monitoring and therapy in both type 1 and type 2 diabetes have substantially reduced the onset and severity of diabetes-related mortality.[10,47] With much of the progress attributed to improved glycaemic control, individual outcomes are often dependent on enhancing and facilitating selfcare, including monitoring and management of diet, blood glucose concentrations, mental health, and exercise. Thus, identifying and managing behaviours that worsen diabetes control is crucial for health outcomes. Large observational studies confirm that heavy alcohol and drug use is associated with increased all-cause mortality and diabetes-related morbidity across the lifespan. In younger cohorts (<30 years), generally with type 1 diabetes, these morbidity and mortality rates relate to increased presentations for diabetic ketoacidosis and hypoglycaemia,[48] whereas in older adults (>30 years), cardiovascular, cerebrovascular, neuropathic, and renal presentations predominate.[49] Clinical conditions for which specific substances and diabetes are independently established risk factors, such as alcohol and peripheral neuropathy, or stimulants and cardiovascular or cerebrovascular events, are of particular concern.[7]

Health-care use

Several case series and larger studies of electronic medical records confirm that patients with comorbid diabetes and substance use disorders are substantial users of health-care systems with high associated health-care costs.[38,50,51] Although most evident for heavy alcohol consumption and intravenous drug use, even low levels of alcohol intake are associated with reduced diabetes self-care behaviours, reduced attendance for diabetes complications screening, and lower engagement with other aspects of diabetes-related care.[36,52] People with type 2 diabetes who have been prescribed opioids also participate

less in screening programmes for diabetes-related complications and have higher HbA_{1c} concentrations when compared with those not prescribed opioids.[53]

Type 1 diabetes, type 2 diabetes, and mortality

Having a diagnosis of a substance use disorder confers an increased all-cause mortality in populations with diabetes across a range of substances including alcohol (OR 1·35, 95% CI 1·19–1·53), cocaine (1·61, 1·21–2·14), opioids (1·35, 1·02–1·8), and cannabis (1·49, 0·94–2·35), regardless of consumption.[54] This mortality is reflected in the disproportionate number of organ transplant donors with diabetes who have detectable amounts of alcohol or drugs in their blood at the time of death.[55]

In a meta-analysis of 26 studies, the relative risk of mortality for people diagnosed with type 1 diabetes was 3·82 (95% CI 3·41–4·29).[56] The contribution of alcohol and other drugs to this mortality gap appears to be substantial.[48,57,58] A Finnish national study that collected data between 1970 and 1999 and included 17 306 people with type 1 diabetes (<30 years), showed a standardised mortality rate for alcohol-related deaths of 1·5 (95% CI 1·1–1·9).[59] In the cohort diagnosed between ages 15 years and 29 years, 39% of deaths in the first 20 years since diagnosis were considered alcohol or drug related.[59]

In a large clinical trial of oral glucose lowering medications in people with type 2 diabetes, the mortality for alcohol consumption followed a U-shape relationship, with the lowest risk being in those with moderate (≤21 standard drinks for men and 14 standard drinks women) alcohol consumption.[49] However, the accumulated risk of heavier drinking appears to be much greater than for the general population. A Finnish prospective observational study involving 434 629 individuals (enrolled between 1997 and 2010) followed for 7·1 years documented a substantially elevated risk of alcohol-related deaths in participants with diabetes compared with controls matched for alcohol consumption. The mortality rate ratio for an alcohol-related death in men with diabetes was 1·71 (95% CI 1·56–1·89) and in women was 2·10 (1·70–2·58), with rates increasing to 6·92 (6·14–7·80) and 10·60 (8·14–13·79) if participants were taking insulin. In the study, 45% of alcohol-related deaths were attributable to liver cirrhosis with non-alcoholic fatty liver disease likely to be a relevant contributor to end-stage liver disease.[60]

Type 1 diabetes and morbidity

The direct metabolic interactions of alcohol with blood glucose are frequently observed by both people with type 1 diabetes and the clinicians who work with them. Alcohol intake causes delayed hypoglycaemia with an onset typically 6–8 h after consumption, the so-called night after evening effect,[61–63] and exacerbates hypoglycaemic unawareness (panel 1).[64,65] Alcohol is metabolised to acetaldehyde, a preferred energy substrate in the gluconeogenic pathway, which is in turn metabolised to acetate. This process increases NADH and decreases NAD+ concentrations, reducing the availability of NAD+ to act as a cofactor for gluconeogenesis.[66] Alcohol also inhibits growth hormone release that can further reduce gluconeogenesis. Hepatic glucose production is initially maintained by glycogenolysis but delayed hypoglycaemia can occur in the setting of alcohol intake, insufficient carbohydrate, and insulin.[63] Alcohol intake is a substantial contributor to hypoglycaemia, with a detectable blood alcohol level in 17% of a cohort of hospital presentations for hypoglycaemia in people with type 1 diabetes.[67]

Illicit drugs have been linked to morbidity in type 1 diabetes. Recurrent diabetic ketoacidosis is a behavioural marker for psychiatric morbidity, with substance use frequently comorbid with other factors including depression, eating disorders, and anxiety.[68] Numerous case series have also linked hospital presentations for diabetic ketoacidosis to cocaine and other stimulant use.[69,70] These case series show a spike in diabetic ketoacidosis presentations at times of increased community cocaine use, consistent with the predicted physiological effects of cocaine and other stimulant-like drugs, such as amphetamine, meth-`amphetamine, and ecstasy (or MDMA) on glucose metabolism. Through the release of peripheral catecholamines, stimulants increase glucose production and inhibit glucose clearance, which increases the risk of hyperglycaemia and, in the setting of relative deficiency of exogenous insulin, the development of ketoacidosis.[71] An association between recent recreational cannabis consumption and a more than double the risk of ketoacidosis has been reported from jurisdictions where cannabis has been legalised.[72,73] This association might relate to emerging higher potency formulations of cannabis and other synthetic cannabinoids although the mechanism remains unclear.

Type 2 diabetes and morbidity

Similar to mortality data, diabetes-related morbidity follows a U-shaped relationship, with people who have type 2 diabetes and consume moderate amounts of alcohol having the lowest incidence of both macrovascular and microvascular complications.[74,75] These data are supported by a single unblinded, 2-year, prospective study that randomly assigned 224 people with type 2 diabetes to 150 mL of white wine, red wine, or sparkling water. The study showed a modest improvement of fasting glucose concentrations in the white wine group (–1·0 mmol/L [95% CI –1·60 to –0·3]; or 17·2 mg/dL [–5·5 to 28·9]) and a favourable improvement in lipid profile in the red wine group (HDL increase by 0·05 mmol/L [95% CI 0·04–0·06 mmol/L]), with no changes in blood pressure, liver function tests, or waist circumference.[76] However, higher levels of alcohol intake and having an alcohol or other substance use disorder contribute substantially to the progression of diabetes-related complications.[77] A matched electronic medical records study that included

8120 participants with type 2 diabetes and an alcohol use disorder showed an OR of 1·35 (95% CI 0·92–1·98) for cerebrovascular accident, 1·27 (1·10–1·46) for diabetic neuropathy, and 1·62 (1·06–2·47) for myocardial infarction compared with people with type 2 diabetes without an alcohol use disorder.[54] A large Finnish study that tracked microvascular complications showed that drinkers who consumed spirits had a higher risk of retinopathy (2·32, 1·35–4·00) and nephropathy in men (2·80, 1·15–6·81).[78] One survey showed that up to 5% of people with diabetes-related eye disease reported occasional binge drinking, a finding the authors suggest raises concern about road safety for this subgroup.[79] Higher prevalence of diabetes-related lower limb amputations in those with a substance use disorder has also been documented.[80]

People with diabetes are at an elevated risk of iatrogenic opioid dependence because of the development of chronic painful conditions, such as peripheral vascular disease and diabetic neuropathy.[53,81] Opioids at commencement might cause hypoglycaemia, which, although the incidence is unclear, is most commonly reported in women and people with diabetes.[82] Crucially, as the total daily dose of prescribed opioids increases, diabetes-related outcomes, including hospital admissions, worsen compared with either no or lower doses of prescribed opioids.[41,53] Furthermore, for those with diabetes and an opioid use disorder, there is a higher risk of cerebrovascular accident (OR 1·94, 95% CI 1·18–3·18) and myocardial infarction (2·01, 1·21–3·36), compared with people with diabetes without an opioid use disorder. Hypogonadism is a well established complication of opioid use with estimates of prevalence varying between 21% and 86% for long-term opioid users.[83] Independently, up to a third of people with type 2 diabetes are also hypogonadal.[84] The prescribing of opioids to people with type 2 diabetes is likely to compound the negative effect of diabetes on erectile dysfunction. This combination might also affect adipose tissue distribution and osteoporosis, although specific studies in this area are scarce.[84]

The risk of a stimulant-induced cerebrovascular or cardiovascular event is elevated in both type 1 and type 2 diabetes. Those with diabetes who have a cocaine use disorder have an increased risk of stroke (OR 2·67, 95% CI 1·75–4·07) and myocardial infarction (2·68, 1·60–4·48).[54] People who are diagnosed with stimulant-induced strokes and myocardial infarctions are typically 15 years younger and less likely to have traditional cardiovascular risk factors, such as diabetes, than those who do not use stimulants.[85] Whether the addition of stimulant use has an additive or synergistic effect on the cardiovascular risk of diabetes is unclear.

Although studies are scarce, no conclusive data show a difference in fasting or postprandial glucose concentrations and HbA_{1c} in people with diabetes, with or without substance use disorders.[86] This finding raises the likelihood that much of the observed mortality and morbidity might not be related to glycaemic control per se, but to the combined effect of the substances on complications and behavioural and environmental risk factors.

Management

Management guidelines for alcohol and drug consumption generally advise the same precautions for people with or without diabetes.[87–89] Although people with type 2 diabetes who drink alcohol at low risk levels (variably defined in national guidelines but typically less than 20 g alcohol daily) should not necessarily be advised to quit alcohol, encouraging people who do not drink to commence alcohol intake for its cardiometabolic benefit is not recommended.[87,89] Considering the uncertain benefits of low-level drinking and clear harm associated with increased alcohol intake, inadvertently promoting alcohol consumption is likely to affect negatively on other health and social outcomes and negate any putative benefit. People with diabetes need to be aware of the effect of binge drinking and regular heavy alcohol intake on their health outcomes. Studies have begun to assess the effectiveness of drug and alcohol interventions for people with diabetes and substance use disorders, although the data at this stage are limited.[90,91]

People are unlikely to spontaneously report their alcohol or drug use to clinicians, and just as for the general population, systematic screening for excess alcohol and drug use is recommended. There might be reasons for people with diabetes to minimise substance use, including stigma, shame, diabetes distress, and concern about access to new technologies. The efficacy of screening for alcohol consumption is better established than for drug use. Screening is done by enquiring about the quantity and frequency of alcohol consumption and episodes of binge drinking,[92] followed by a brief intervention (short counselling sessions usually lasting less than 15 min) and referral for treatment as required (known as screening, brief intervention, and referral for treatment or SBIRT). Several studies have established the effectiveness of SBIRT in people with type 1 or type 2 diabetes.[91,93] One study combined measurement of carbohydrate-deficient transferrin, a biomarker of alcohol consumption, with a brief intervention in a primary care population with type 2 diabetes or hypertension, resulting in a reduction of reported heavy drinkers from 35·8% to 24·7% over 12 months.[94]

Harm reduction advice has an important role in younger cohorts (panel 2). The most effective advice depends on the age, geographical location, and particular substance in question, but should include the risk of alcohol-related delayed hypoglycaemia for all patients on insulin or insulin secretagogues.[95] Several studies have established a gap between knowledge of the effect of alcohol on blood glucose control and application in a real-life social context.[33,96] In one study, although 95% of adolescents with type 2 diabetes reported that they knew they should check their blood glucose in the middle of

the night after drinking, only 62% reported doing this in practice.[96] In another study, adults with type 1 diabetes stated that they were more likely to make planned insulin adjustments for exercise than for alcohol consumption.[97] Attempts have been made to establish the most acceptable and actionable harm reduction advice, with one study noting that avoiding drinking games and pacing one's drinking were associated with less alcohol-related harm, than relying on a friend to advise when to stop drinking or to eat regular carbohydrate containing snacks.[98] Both traditional continuous and flash glucose monitoring might provide important real-time feedback. Further research is required to help to identify the most effective harm reduction strategies.

Intensive psychosocial interventions to modify substance use appear to be similarly efficacious in people with and without diabetes. Although integrated care models, active case finding, and streamlined referrals to psychiatric and social services have been shown to be effective for comorbid depression and diabetes,[99,100] similar trials have not yet been done for substance use disorders, but these approaches could be beneficial. In groups at the highest risk, intensive interventions including case management and residential rehabilitation reduce both substance use and improve diabetes-related outcomes across age groups and diabetes types.[90,101] These might be provided in both outpatient and residential settings, and include motivational interviewing, cognitive behaviour therapy, peer led 12-step based therapies such as alcoholics or narcotic anonymous, mindfulness based interventions, acceptance and commitment therapy, and contingency management.[101] Pharmacological treatments for alcohol use disorders, including naltrexone, acamprosate, and disulfiram could be prescribed with no specific contraindications or precautions for people with diabetes.

For people with type 2 diabetes and opioid use disorders, opioid agonist therapies are of benefit. One study documented a mean improvement in HbA_{1c} from 9·8% (83·6 mmol/mol) to 8·6% (70·5) in 62 Canadian First Nations people with comorbid type 2 diabetes and opioid use disorders commenced on buprenorphine–naloxone.[102] A small study of 119 patients on opioid agonist treatment showed that those prescribed methadone were 3·4 times more likely to have diabetes than those on buprenorphine. This finding suggests that methadone adversely affects blood glucose metabolism and that buprenorphine might be the preferred option for this cohort.[45]

Limitations

Ethical and practical concerns often restrict research in the area of alcohol and drug use to observational studies. Since most of the research includes secondary analyses of routine medical registers or other health surveys, determining whether an association detected is the result of a direct physiological effect of a substance or an associated behaviour, non-adherence to treatment, socioeconomic factors, comorbid mental health conditions, reporting bias, or diagnostic misclassification can be difficult.

Established associations might quickly lose relevance because of fluctuating patterns of substance use. The environmental context and legal framework within which substances are consumed can affect the type, quantity, and potency of substances used and reported. The volume of data that examine the relationship between alcohol consumption and, to some extent, prescription opioids is far greater than that for illicit drugs. Furthermore, reliable data might quickly become outdated because of changing patterns of substance use in the population being studied (eg, substantial differences would be expected to exist between cohorts using prescribed opioids for chronic pain and people consuming illicit intravenous diamorphine heroin). However, as individuals become dependent on prescribed opioids, they might progress to using heroin and other injectable unsanctioned opioids, thus, contaminating the two groups epidemiologically. Cannabis presents a concern as strains of cannabis have changed over the previous decades and now generally contain higher amounts of tetrahydrocannabinol. Despite a limited evidence base, medicinal cannabis is being promoted by some for the treatment of diabetic neuropathic pain.[103] The actual quantity and proportion of cannabinoids in the final substance consumed might be unclear and could account for the variation in research findings.[103] As the background values for substance use evolve, the effect on people with diabetes will need to be re-assessed.

Search strategy and selection criteria

We searched MEDLINE, CINAHL, Embase, Emcare, PsycINFO, and Cochrane for articles published between Jan 1, 2000, and Oct 15, 2019, with no language restrictions. Our subject and title search terms were "diabetes mellitus", "type 1 diabetes" or "type 2 diabetes" in combination with terms relevant to alcohol or recreational illicit drug use such as "substance related disorders", "alcohol-related disorders", "alcohol-induced disorders", "marijuana", "cannabis" "opioid related disorders", "substance abuse", or "amphetamines." We also searched the reference list of identified articles for earlier published frequently referenced studies. We mainly selected articles that were large observational studies, randomised trials, or meta-analyses.

Conclusion

Substance use and diabetes are both major contributors to the global burden of disease. They frequently coexist and present throughout the health system including primary care, emergency departments, specialist endocrinology, and addiction medicine services. People with diabetes who have substance use disorders endure disproportionate effects on both morbidity and mortality. Excess drinking carries substantially poorer outcomes across a

range of measures relative to the general population. For occasional illicit drug users, rare but catastrophic health outcomes are considerably more common.

Clinicians working with people who have diabetes should routinely screen for alcohol and illicit drugs, provide focused harm reduction messages, and understand that treatment approaches for substance use are equally efficacious in people with diabetes as in those without diabetes. Clinicians should give close and thoughtful attention to people with diabetes who are frequently admitted to hospital or if there are concerns regarding self-management. For younger people with type 1 or type 2 diabetes in whom substance use, particularly experimental or episodic, is more common, harm reduction measures might help avert catastrophic complications. Brief interventions are effective for alcohol use, but those with substance use disorders are likely to require more intensive interventions and collaboration with addiction specialists.

Contributors

AP searched the literature. AP and YB wrote the initial draft of the Review. JC, RJM, and YB critically revised and edited the Review. All authors approved the final submission.

Declaration of interests

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References

1 IDF. IDF diabetes atlas, 8th edn. Brussels: International Diabetes Federation, 2017.

2 GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018; **392:** 1015–35.

3 GBD 2016 Alcohol Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry* 2018; **5:** 987–1012.

4 Dowell D, Arias E, Kochanek K, et al. Contribution of opioid-involved poisoning to the change in life expectancy in the United States, 2000–2015. *JAMA* 2017; **318:** 1065–67.

5 Grant BF, Saha TD, Ruan WJ, et al. Epidemiology of DSM-5 drug use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry* 2016; **73:** 39–47.

6 Ghitza UE, Wu LT, Tai B. Integrating substance abuse care with community diabetes care: implications for research and clinical practice. *Subst Abuse Rehabil* 2013; **4:** 3–10.

7 Walter KN, Wagner JA, Cengiz E, Tamborlane WV, Petry NM. Substance use disorders among patients with type 2 diabetes: a dangerous but understudied combination. *Curr Diab Rep* 2017; **17:** 2.

8 AAP. Diagnostic and statistical manual of mental disorders, 5th ed. Arlington, VA: American Psychiatric Association, 2013.

9 WHO. ICD-10: international statistical classification of diseases and related health problems, tenth revision, 2nd edn. Geneva: World Health Organization, 2004.

10 DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet* 2018; **391:** 2449–62.

11 Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. *Diabetes Care* 2003; **26:** 2785–90.

12 Knott C, Bell S, Britton A. Alcohol consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of more than 1·9 million individuals from 38 observational studies. *Diabetes Care* 2015; **38:** 1804–12.

13 Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018; **391:** 1513–23.

14 Kerr WC, Ye Y, Williams E, Lui CK, Greenfield TK, Lown EA. Lifetime alcohol use patterns and risk of diabetes onset in the national alcohol survey. *Alcohol Clin Exp Res* 2019; **43:** 262–69.

15 Huang J, Wang X, Zhang Y. Specific types of alcoholic beverage consumption and risk of type 2 diabetes: a systematic review and meta-analysis. *J Diabetes Investig* 2017; **8:** 56–68.

16 Sluik D, Jankovic N, Hughes M, et al. Alcoholic beverage preference and diabetes incidence across Europe: the Consortium on Health and Ageing Network of Cohorts in Europe and the United States (CHANCES) project. *Eur J Clin Nutr* 2017; **71:** 659–68.

17 Schrieks IC, Heil AL, Hendriks HF, Mukamal KJ, Beulens JW. The effect of alcohol consumption on insulin sensitivity and glycemic status: a systematic review and meta-analysis of intervention studies. *Diabetes Care* 2015; **38:** 723–32.

18 Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 2011; **342:** d636.

19 Tatsumi Y, Morimoto A, Asayama K, et al. Association between alcohol consumption and incidence of impaired insulin secretion and insulin resistance in Japanese: the Saku study. *Diabetes Res Clin Pract* 2018; **135:** 11–17.

20 Yoo MG, Kim HJ, Jang HB, Lee HJ, Park SI. The association between alcohol consumption and β-cell function and insulin sensitivity in Korean population. *Int J Environ Res Public Health* 2016; **13:** e1133.

21 Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008; **31:** 2383–90.

22 Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: mendelian randomisation analysis based on individual participant data. *BMJ* 2014; **349:** g4164.

23 Millwood IY, Walters RG, Mei XW, et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. *Lancet* 2019; **393:** 1831–42.

24 Imtiaz S, Rehm J. The relationship between cannabis use and diabetes: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *Drug Alcohol Rev* 2018; **37:** 897–902.

25 Rajavashisth TB, Shaheen M, Norris KC, et al. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. *BMJ Open* 2012; **2:** e000494.

26 Muniyappa R, Sable S, Ouwerkerk R, et al. Metabolic effects of chronic cannabis smoking. *Diabetes Care* 2013; **36:** 2415–22.

27 Bancks MP, Pletcher MJ, Kertesz SG, Sidney S, Rana JS, Schreiner PJ. Marijuana use and risk of prediabetes and diabetes by middle adulthood: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetologia* 2015; **58:** 2736–44.

28 Danielsson AK, Lundin A, Yaregal A, Östenson CG, Allebeck P, Agardh EE. Cannabis use as risk or protection for type 2 diabetes: a longitudinal study of 18 000 Swedish men and women. *J Diabetes Res* 2016; **2016:** 6278709.

29 Li L, Setoguchi S, Cabral H, Jick S. Opioids and risk of type 2 diabetes in adults with non-cancer pain. *Pain Physician* 2013; **16:** 77–88.

30 Petry NM, Foster NC, Cengiz E, Tamborlane WV, Wagner J, Polsky S. Substance use in adults with type 1 diabetes in the T1D exchange. *Diabetes Educ* 2018; **44:** 510–18.

31 Potter K, Luca P, Pacaud D, et al. Prevalence of alcohol, tobacco, cannabis and other illicit substance use in a population of Canadian adolescents with type 1 diabetes compared to a general adolescent population. *Paediatr Child Health* 2018; **23:** 185–90.

32 Hanna KM, Stupiansky NW, Weaver MT, Slaven JE, Stump TE. Alcohol use trajectories after high school graduation among emerging adults with type 1 diabetes. *J Adolesc Health* 2014; **55:** 201–08.

33 Barnard KD, Dyson P, Sinclair JM, et al. Alcohol health literacy in young adults with type 1 diabetes and its impact on diabetes management. *Diabet Med* 2014; **31:** 1625–30.

34 Jakobsen ML, Larsen JR, Glümer C, et al. Alcohol consumption among patients with diabetes: a survey-based cross-sectional study of Danish adults with diabetes. *Scand J Public Health* 2016; **44:** 517–24.

35 Kerr WC, Ye Y, Greenfield TK, et al. Changes in heavy drinking following onset of health problems in a US general population sample. *Prev Med* 2017; **95:** 47–51.

36 Ahmed AT, Karter AJ, Liu J. Alcohol consumption is inversely associated with adherence to diabetes self-care behaviours. *Diabet Med* 2006; **23:** 795–802.

37 Wu LT, Ghitza UE, Batch BC, et al. Substance use and mental diagnoses among adults with and without type 2 diabetes: results from electronic health records data. *Drug Alcohol Depend* 2015; **156:** 162–69.

38 Wu LT, Ghitza UE, Zhu H, Spratt S, Swartz M, Mannelli P. Substance use disorders and medical comorbidities among high-need, high-risk patients with diabetes. *Drug Alcohol Depend* 2018; **186:** 86–93.

39 King WC, Chen JY, Courcoulas AP, et al. Alcohol and other substance use after bariatric surgery: prospective evidence from a US multicenter cohort study. *Surg Obes Relat Dis* 2017; **13:** 1392–402.

40 Blackburn AN, Hajnal A, Leggio L. The gut in the brain: the effects of bariatric surgery on alcohol consumption. *Addict Biol* 2017; **22:** 1540–53.

41 Gautam S, Franzini L, Mikhail OI, Chan W, Turner BJ. Longitudinal analysis of opioid analgesic dose and diabetes quality of care measures. *Pain Med* 2015; **16:** 2134–41.

42 Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ* 2014; **348:** g1251.

43 King WC, Chen JY, Belle SH, et al. Use of prescribed opioids before and after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. *Surg Ober Relat Dis* 2017; **13:** 1337–46.

44 Vancampfort D, Mugisha J, Hallgren M, et al. The prevalence of diabetes mellitus type 2 in people with alcohol use disorders: a systematic review and large scale meta-analysis. *Psychiatry Res* 2016; **246:** 394–400.

45 Fareed A, Byrd-Sellers J, Vayalapalli S, Drexler K, Phillips L. Predictors of diabetes mellitus and abnormal blood glucose in patients receiving opioid maintenance treatment. *Am J Addict* 2013; **22:** 411–16.

46 Howard AA, Hoover DR, Anastos K, et al. The effects of opiate use and hepatitis C virus infection on risk of diabetes mellitus in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2010; **54:** 152–59.

47 Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet* 2017; **389:** 2239–51.

48 Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. *Diabetes Care* 2005; **28:** 1618–23.

49 Blomster JI, Zoungas S, Chalmers J, et al. The relationship between alcohol consumption and vascular complications and mortality in individuals with type 2 diabetes. *Diabetes Care* 2014; **37:** 1353–59.

50 Saunders SA, Democratis J, Martin J, Macfarlane IA. Intravenous drug abuse and type 1 diabetes: financial and healthcare implications. *Diabet Med* 2004; **21:** 1269–73.

51 Leung KS, Parks J, Topolski J. Preventable hospitalizations among adult Medicaid beneficiaries with concurrent substance use disorders. *Prev Med Rep* 2015; **2:** 379–84.

52 Thomas RM, Francis Gerstel PA, Williams EC, et al. Association between alcohol screening scores and diabetic self-care behaviors. *Fam Med* 2012; **44:** 555–63.

53 Rose AJ, Hermos JA, Frayne SM, Pogach LM, Berlowitz DR, Miller DR. Does opioid therapy affect quality of care for diabetes mellitus? *Am J Manag Care* 2009; **15:** 217–24.

54 Winhusen T, Theobald J, Kaelber DC, Lewis D. Medical complications associated with substance use disorders in patients with type 2 diabetes and hypertension: electronic health record findings. *Addiction* 2019; **114:** 1462–70.

55 Jacobsen LM, Haller MJ, Parish A, et al. High illicit drug abuse and suicide in organ donors with type 1 diabetes. *Diabetes Care* 2017; **40:** e122–23.

56 Lung TW, Hayes AJ, Herman WH, Si L, Palmer AJ, Clarke PM. A meta-analysis of the relative risk of mortality for type 1 diabetes patients compared to the general population: exploring temporal changes in relative mortality. *PLoS One* 2014; **9:** e113635.

57 Gagnum V, Stene LC, Leivestad T, Joner G, Skrivarhaug T. Long-term mortality and end-stage renal disease in a type 1 diabetes population diagnosed at age 15–29 years in Norway. *Diabetes Care* 2017; **40:** 38–45.

58 Feltbower RG, Bodansky HJ, Patterson CC, et al. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of diabetes in children and young adults. *Diabetes Care* 2008; **31:** 922–26.

59 Harjutsalo V, Forsblom C, Groop P-H. Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *BMJ* 2011; **343:** d5364.

60 Niskanen L, Partonen T, Auvinen A, Haukka J. Excess mortality in Finnish diabetic subjects due to alcohol, accidents and suicide: a nationwide study. *Eur J Endocrinol* 2018; **179:** 299–306.

61 Turner BC, Jenkins E, Kerr D, Sherwin RS, Cavan DA. The effect of evening alcohol consumption on next-morning glucose control in type 1 diabetes. *Diabetes Care* 2001; **24:** 1888–93.

62 Hirst JA, Aronson JK, Feakins BG, Ma C, Farmer AJ, Stevens RJ. Short- and medium-term effects of light to moderate alcohol intake on glycaemic control in diabetes mellitus: a systematic review and meta-analysis of randomized trials. *Diabet Med* 2017; **34:** 604–11.

63 Tetzschner R, Nørgaard K, Ranjan A. Effects of alcohol on plasma glucose and prevention of alcohol-induced hypoglycemia in type 1 diabetes: a systematic review with GRADE. *Diabetes Metab Res Rev* 2018; **34:** e2965.

64 Kerr D, Cheyne E, Thomas P, Sherwin R. Influence of acute alcohol ingestion on the hormonal responses to modest hypoglycaemia in patients with Type 1 diabetes. *Diabet Med* 2007; **24:** 312–16.

65 Cheyne EH, Sherwin RS, Lunt MJ, Cavan DA, Thomas PW, Kerr D. Influence of alcohol on cognitive performance during mild hypoglycaemia; implications for Type 1 diabetes. *Diabet Med* 2004; **21:** 230–37.

66 Plougmann S, Hejlesen O, Turner B, Kerr D, Cavan D. Modelling the effect of alcohol in type 1 diabetes. *Stud Health Technol Inform* 2002; **90:** 66–71.

67 Pedersen-Bjergaard U, Reubsaet JL, Nielsen SL, et al. Psychoactive drugs, alcohol, and severe hypoglycemia in insulin-treated diabetes: analysis of 141 cases. *Am J Med* 2005; **118:** 307–10.

68 Garrett CJ, Choudhary P, Amiel SA, Fonagy P, Ismail K. Recurrent diabetic ketoacidosis and a brief history of brittle diabetes research: contemporary and past evidence in diabetic ketoacidosis research including mortality, mental health and prevention. *Diabet Med* 2019; **36:** 1329–35.

69 Nyenwe EA, Loganathan RS, Blum S, et al. Active use of cocaine: an independent risk factor for recurrent diabetic ketoacidosis in a city hospital. *Endocr Pract* 2007; **13:** 22–29.

70 Isidro ML, Jorge S. Recreational drug abuse in patients hospitalized for diabetic ketosis or diabetic ketoacidosis. *Acta Diabetol* 2013; **50:** 183–87.

71 Lee P, Greenfield JR, Campbell LV. Managing young people with type 1 diabetes in a 'rave' new world: metabolic complications of substance abuse in type 1 diabetes. *Diabet Med* 2009; **26:** 328–33.

72 Akturk HK, Taylor DD, Camsari UM, Rewers A, Kinney GL, Shah VN. Association between cannabis use and risk for diabetic ketoacidosis in adults with type 1 diabetes. *JAMA Intern Med* 2019; **179:** 115–18.

73 Kinney GL, Akturk HK, Taylor DD, Foster NC, Shah VN. Cannabis use is associated with increased risk for diabetic ketoacidosis in adults with type 1 diabetes: findings from the T1D Exchange Clinic Registry. *Diabetes Care* 2019; dc190365.

74 Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. Meta-analysis of the relationship between alcohol consumption and coronary heart disease and mortality in type 2 diabetic patients. *Diabetologia* 2006; **49:** 648–52.

75 Beulens JW, Kruidhof JS, Grobbee DE, Chaturvedi N, Fuller JH, Soedamah-Muthu SS. Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: the EURODIAB Prospective Complications Study. *Diabetologia* 2008; **51:** 1631–38.

76 Gepner Y, Golan R, Harman-Boehm I, et al. Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: a 2-year randomized, controlled trial. *Ann Intern Med* 2015; **163:** 569–79.

77 Schmidt EM, Barnes J, Chen C, Trafton J, Frayne S, Harris AHS. Patient and health care factors associated with long-term diabetes complications among adults with and without mental health and substance use disorders. *JAMA Netw Open* 2019; **2:** e1912060.

78 Harjutsalo V, Feodoroff M, Forsblom C, Groop PH. Patients with type 1 diabetes consuming alcoholic spirits have an increased risk of microvascular complications. *Diabet Med* 2014; **31:** 156–64.

79 Mukamal KJ. Hazardous drinking among adults with diabetes and related eye disease or visual problems: a population-based cross-sectional survey. *Ophthalmic Epidemiol* 2007; **14:** 45–49.

80 Leung G, Zhang J, Lin WC, Clark RE. Behavioral disorders and diabetes-related outcomes among Massachusetts Medicare and Medicaid beneficiaries. *Psychiatr Serv* 2011; **62:** 659–65.

81 Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 2015; **156:** 569–76.

82 Chrétien B, Dolladille C, Hamel-Sénécal L, et al. Comparative study of hypoglycaemia induced by opioids. Is it a class effect? *Expert Opin Drug Saf* 2019; **18:** 987–92.

83 Fountas A, Chai ST, Kourkouti C, Karavitaki N. Mechanisms of endocrinology: endocrinology of opioids. *Eur J Endocrinol* 2018; **179:** R183–96.

84 Dhindsa S, Ghanim H, Batra M, Dandona P. Hypogonadotropic hypogonadism in men with diabesity. *Diabetes Care* 2018; **41:** 1516–25.

85 DeFilippis EM, Singh A, Divakaran S, et al. Cocaine and marijuana use among young adults with myocardial infarction. *J Am Coll Cardiol* 2018; **71:** 2540–51.

86 Ojo O, Wang XH, Ojo OO, Ibe J. The effects of substance abuse on blood glucose parameters in patients with diabetes: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2018; **15:** e2691.

87 American Diabetes Association. Lifestyle management: standards of medical care in diabetes–2019. *Diabetes Care* 2019; **42** (suppl 1)**:** S46–60.

88 Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2018; **61:** 2461–98.

89 NICE. Type 2 diabetes in adults: management. London: 2019.

90 Svoren BM, Butler D, Levine BS, Anderson BJ, Laffel LM. Reducing acute adverse outcomes in youths with type 1 diabetes: a randomized, controlled trial. *Pediatrics* 2003; **112:** 914–22.

91 Ramsey SE, Engler PA, Harrington M, et al. Brief alcohol intervention among at-risk drinkers with diabetes. *Subst Abuse* 2010; **4:** 1–8.

92 Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. Project ftACQI. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *JAMA Intern Med* 1998; **158:** 1789–95.

93 Tanner-Smith EE, Risser MD. A meta-analysis of brief alcohol interventions for adolescents and young adults: variability in effects across alcohol measures. *Am J Drug Alcohol Abuse* 2016; **42:** 140–51.

94 Fleming M, Brown R, Brown D. The efficacy of a brief alcohol intervention combined with %CDT feedback in patients being treated for type 2 diabetes and/or hypertension. *J Stud Alcohol* 2004; **65:** 631–37.

95 Pastor A, O'Brien CL, Teng J, et al. Experiences of young adults with type 1 diabetes while using alcohol and recreational drugs: an interpretative phenomenological analysis (IPA) of semi-structured interviews. *Diabetes Res Clin Pract* 2018; **141:** 47–55.

96 Potter K, Virtanen H, Luca P, et al. Knowledge and practice of harm-reduction behaviours for alcohol and other illicit substance use in adolescents with type 1 diabetes. *Paediatr Child Health* 2019; **24:** e51–56.

97 Grando MA, Groat D, Soni H, et al. Characterization of exercise and alcohol self-management behaviors of type 1 diabetes patients on insulin pump therapy. *J Diabetes Sci Technol* 2017; **11:** 240–46.

98 Ravert RD. Alcohol management strategies of college students with diabetes. *Patient Educ Couns* 2009; **77:** 97–102.

99 Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010; **363:** 2611–20.

100 Ismail K, Stewart K, Ridge K, et al. A pilot study of an integrated mental health, social and medical model for diabetes care in an inner-city setting: three dimensions for diabetes (3DFD). *Diabet Med* 2019; published online Feb 1. DOI:10.1111/dme.13918.

101 Walter KN, Petry NM. Patients with diabetes respond well to contingency management treatment targeting alcohol and substance use. *Psychol Health Med* 2015; **20:** 916–26.

102 Tilbrook D, Jacob J, Parsons P, Edwards C, Loewen K, Kelly L. Opioid use disorder and type 2 diabetes mellitus: effect of participation in buprenorphine-naloxone substitution programs on glycemic control. *Can Fam Physician* 2017; **63:** e350–54.

103 National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.