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Diabetes and Alcohol

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INTRODUCTION

Studies in the general population show an improvement in mortality and morbidity from light to moderate ingestion of alcohol. This improved mortality was greatest amongst those individuals with the highest risk of ischaemic heart disease (1). The definition of light to moderate intake is, however, confusing and varies between researchers from one to three drinks per day, 3–4 units for men and 2–3 units for women per day, 0.5–1.0 g/kg body weight, or 'moderate drinking is the level below which overall net harmful effects are seen in population surveys, about three drinks per day. Thus less than three drinks per day is moderate or lighter drinking and heavy drinking is three or more drinks per day' (2).

Recommendations have generally been determined from epidemiological and retrospective data where the problem of evaluating thresholds is complicated by the underestimation of alcohol consumption. Drinking more frequently or larger measures than reported can lead to a lower apparent threshold of alcohol-related effects.

For people with diabetes, recommendations for alcohol intakes are complicated by the well-established risks of alcohol ingestion such as increasing blood pressure, increasing triglycerides and contributing to obesity versus the benefits of reducing the risk of ischaemic heart disease through increasing HDL cholesterol, increasing insulin sensitivity and the contribution of antioxidant nutrients. (The effect of alcohol ingestion on these individual risks and benefits is discussed later in this chapter.)

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NUTRITIONAL RECOMMENDATIONS

For the general adult population 'sensible' limits are 21 units per week or 2–3 units per day for men and 14 units per week or 1–2 units per day for women. This remains the recommendation by the Royal College of Physicians despite the Department of Health increasing the recommended number of units to 28 and 21 units per week, respectively (3).

The current European nutritional recommendations for people with diabetes (1999) state 'For those who choose to drink alcohol, intakes of up to 15 g for women and 30 g for men are acceptable' per day (4,5). This equates to one small (125 ml) glass of wine (12% abv) or 1.5 units for women per day and two small glasses of wine (12% abv) for men, which equates to 3 units. However, many wines have a higher alcohol content and many people would regularly drink a larger measure. The present consensus outlined in the European and American nutritional recommendations for people with diabetes concludes that there are benefits (unless medically contraindicated) from light to moderate alcohol intakes taken with a carbohydrate-containing meal. Moderate intakes of wine, especially red wine, which contains non-nutrient flavonoid and phenolic compounds, which have antioxidant properties, may confer greater benefit than consumption of spirits or beer (6). Much of the evidence from studies is based on weekly intakes of alcoholic drinks, but considering that the beneficial effects of moderate drinking on fibrinolytic factors (7) and blood pressure (8) are transient, it is most beneficial to have light to moderate daily intakes. Health professionals should be cautious when advising on intakes because many people underestimate their alcohol consumption. Practical recommendations should be explained in terms of drinks and units to avoid confusion. Table 13.1 shows the alcoholic content and number of units contributed by commonly consumed alcoholic beverages.

PRACTICAL RECOMMENDATIONS

Provided alcohol intakes are not contraindicated (see below), for most people with diabetes it is healthiest for men to drink 2–3 units and women to drink 1–2 units per day. Higher intakes, even taken occasionally, will have an impact on blood pressure and triglycerides and will increase the risk of hypoglycaemia and ketoacidosis.

It is especially important that people with diabetes who are treated with insulin or sulphonylureas should eat a carbohydrate-containing meal and take their medication before drinking and have a bedtime snack (and long-acting insulin if prescribed) before going to sleep. They should also be aware that prolonged and severe hypoglycaemia can occur up to 36 h after binge drinking and this can be mistaken for intoxication. For those inclined to drink more

Table 13.1 The alcoholic content and number of units contributed by commonly consumed alcoholic drinks

Drink	Measure	No. of units	Alcohol (g)
Beers, lagers and cider			
3–5% abv	250 ml (0.5 pt)	0.75–1.25	7.5–12.5
	500 ml (1 pt)	1.5–2.5	15–25
6–8% abv	250 ml (0.5 pt)	1.5–2.0	15–20
	500 ml (1 pt)	3.0–4.0	30–40
Wine			
9–11% abv	Sm glass (125 ml)	1.0–1.4	10–14
	Med glass (175 ml)	1.1–2.0	11–20
	Lg glass (250 ml)	2.25–2.75	22.5–27.5
	1 bottle (750 ml)	6.75–8.25	67.5–82.5
12–14% abv	Sm glass (125 ml)	1.5–1.75	15–17.5
	Med glass (175 ml)	2.1–2.45	21–24.5
	Lg glass (250 ml)	3.0–3.5	42–49
	1 bottle (750 ml)	9.0–10.5	90–105
Fortified wines (sherry/port)			
16% abv	50 ml glass	0.8	8
Spirits (vodka/gin/rum, etc.)			
40% abv	25 ml	1.0	10

than the recommended intakes advice should be given on how to minimise the risk of hypoglycaemia. This might include eating carbohydrate-containing snacks that might not be particularly healthy, e.g. savoury snacks like crisps and peanuts or alternating alcoholic drinks with sugar-containing soft drinks or fruit juice.

The normal precautions for alcohol intakes still apply with regard to drinking and driving, but it is obviously very important to minimise the risk of hypoglycaemia.

There is no specific benefit for people with diabetes to consume low-carbohydrate beers/lagers or low-alcohol drinks; it is total alcohol intake, how rapidly it is consumed and whether it is consumed with or after food that will determine its effect.

CONTRAINDICATIONS

People with diabetes who should abstain from drinking alcohol include those with a history of alcohol abuse, pancreatitis, liver disease, gastritis and women during pregnancy. Also intakes should be restricted for those who have hypertriglyceridaemia, hypertension, neuropathy and frequent hypoglycaemia and hyperglycaemia.

People with DM who also take antiepileptics and tranquillisers should seek advice from their doctor or pharmacist before drinking alcohol because of possible drug interactions.

METABOLISM OF ALCOHOL

The liver metabolises alcohol at an average rate of 0.1 g/kg body weight per hour. Thus an average 70 kg man will require 2 h to metabolise 24 g alcohol, the equivalent of 1.5 small glasses of wine. The total quantity and the rate of alcohol ingestion determines its effect (9). Some of the alcohol in the stomach is metabolised by the enzyme alcohol dehydrogenase, which is present in the gastric mucosa. Women have less gastric alcohol dehydrogenase activity than men, so their blood alcohol concentration rises more markedly. Once absorbed the alcohol spreads rapidly into the body water and the smaller size and greater fat content of women amplifies the rise.

Alcohol is metabolised in a series of reactions to acetyl Co A which, in most extra-hepatic tissues, is then channelled into the TCA cycle. Here, it is oxidised and this generates most of the ATP from ethanol oxidation. A small proportion of the acetyl Co A that remains in the liver and that is present in the adipose tissue may act as a precursor for the biosynthesis of fatty acids and glycerol.

OXIDATION OF ETHANOL TO ETHANAL (ACETALDEHYDE)

Most of the absorbed alcohol is taken up by the liver. Here, three separate enzyme reactions oxidise the ethanol to ethanal.

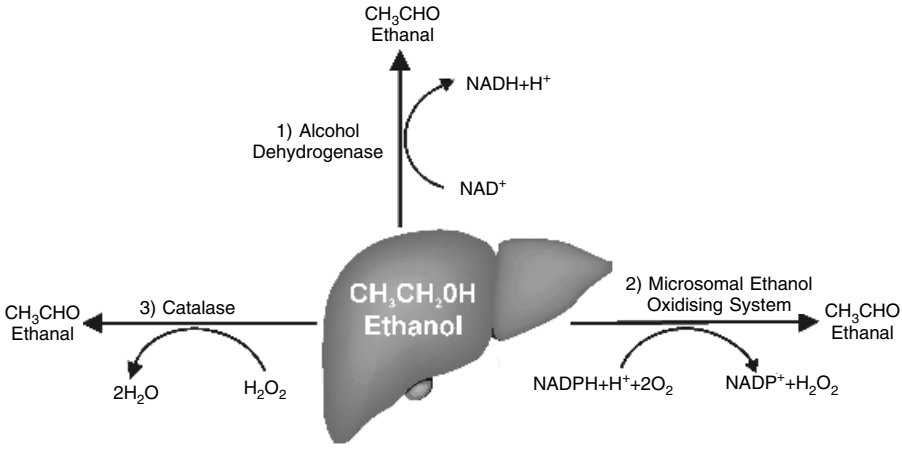

Figure 13.1 Pathway as described by Newsholme and Leech 1990. Reproduced with permission of John Wiley & Sons Limited

Alcohol Dehydrogenase

The reaction catalysed by alcohol dehydrogenase is the most widely known. This enzyme is also present in much smaller amounts in the gastric mucosa, kidney and adipose tissue.

Microsomal Ethanol Oxidising System

This enzyme system uses NADPH and oxygen to catalyse the reaction to ethanal. The enzyme cytochrome P450 is involved in this reaction and also in the detoxification of many drugs. Alcohol competes with these drugs for the enzyme site and its presence, therefore, can lead to higher circulating levels of drugs which may reach toxic levels (10).

Catalase

In the liver peroxisomes, the enzyme catalase reduces H_2O_2 to H_2O concomitantly as it oxidises ethanol to ethanal.

OXIDATION OF ETHANAL TO ACETATE

This reaction is catalysed by aldehyde dehydrogenase:

$$CH_3CHO + NAD^+ + H_2O \rightarrow CH_3COO^- + NADH + 2H^+$$

CONVERSION TO ACETYL Co A

Most of the acetate escapes from the liver and is converted to acetyl Co A in extra-hepatic tissues by the enzyme acetyl Co A synthetase:

$$CH_3COO^- + ATP^{4-} + CoASH \rightarrow CH_3COSCoA + AMP^{3-} + PPi^{3-}$$

The acetyl Co A is then oxidised via the TCA cycle which generates ATP.

REOXIDATION OF NADH AND REDUCTION OF NADPH

NADH is generated in the first two reactions of alcohol metabolism as outlined above. It is necessary for NADH to then be reoxidised to NAD^+ so that it can be involved in further oxidation reactions in the cytosol:

$$NADH \xrightarrow{\text{Reoxidation by the mitochondrial electron transport system}} NAD + H^+$$

The cytosolic NADH is reoxidised by the mitochondrial electron transport system, so substrate shuttles need to be used to transport the H atoms to the mitochondria.

Under some conditions, the rate of transfer of H atoms by these shuttles is less than the rate of NADH generation, so that the concentration of NAD^+ becomes greatly reduced. This low concentration of NAD^+ also restricts the conversion of lactate to pyruvate in the liver. This is one element by which alcohol increases the concentration of lactate in the blood.

The low NAD^+ level limits the rate of ethanol oxidation by alcohol dehydrogenase (the first step in alcohol metabolism). Alcohol decreases the ratio of NAD^+ to NADH within the hepatocyte while it is being oxidised.

METABOLIC AND CLINICAL EFFECTS OF ALCOHOL CONSUMPTION

Evidence suggests that some of the clinical effects of alcohol ingestion are not due to ethanol itself but to its metabolites NADH and ethanal (acetaldehyde). The NAD^+/NADH concentration ratio in the cytosol is maintained at a value of 1000 (11). The administration of alcohol can lower this ratio by at least 10-fold (12). The concentration of all substrates and products which thus use dehydrogenase enzymes will be affected by a change in the NAD^+/NADH concentration ratio. Therefore a reduction of this concentration ratio will lower the concentration of the oxidised reactant and increase that of the reduced reactant. If either of these reactants has an important metabolic role, marked changes in their concentration could produce abnormal effects.

The increased ethanal levels which are seen after alcohol ingestion are further raised if the activity of aldehyde dehydrogenase is inhibited. Inhibitors of the enzyme include the higher aliphatic aldehydes which are known to be present in alcoholic beverages.

The following physiological effects can be, in part, explained by the changes in the NAD^+/NADH ratio.

FATTY LIVER, HEPATITIS AND CIRRHOSIS

Chronic alcohol consumption can cause the deposition of excess triglycerol in the liver leading to a condition known as ‘fatty liver’. This damage can lead to hepatitis and, if severe enough, to cirrhosis. The damage is thought to be due to the high concentrations of ethanal within the cell and if severe enough will result in cell death. Cell damage and death trigger an inflammatory response, i.e. infiltration of lymphocytes and activation of an immune response. If this is not treated it will lead to the formation of fibrous tissue and a severe reduction in the functioning of the liver.

HYPOGLYCAEMIA

In the fasted state, hepatic gluconeogenesis is essential for the production of glucose and maintenance of the blood sugar level. Ethanol is a potent inhibitor of gluconeogenesis. The suppression of gluconeogenesis, even at relatively low alcohol intakes, with low serum insulin and high serum glucagon, results in a decreased ratio of NAD^+ to NADH which inhibits the entry of the precursors of gluconeogenesis (i.e. glycerol, lactate, alanine and other amino acids) into the hepatocyte (13). This can lead to severe and prolonged hypoglycaemia when large volumes of alcohol are ingested rapidly and may occur up to 36 h after alcohol ingestion. The major problem of alcohol ingestion in the person with diabetes is induction and masking of hypoglycaemia, causing hypoglycaemia unawareness.

Hypoglycaemia most commonly occurs in the fasting state in people with Type 1 and Type 2 diabetes but also in non-diabetics, especially when hepatic glycogen stores are depleted or exhausted. Alcohol-induced hypoglycaemia may not be effectively treated by glucagon administration because it is related to depleted glycogen stores. Alcohol consumption leads to delayed glucose recovery from insulin-induced hypoglycaemia in people with Type 1 diabetes, and occurs despite normal adrenalin, nor-adrenalin and glucagon responses, however growth hormone and cortisol are reduced (14).

Hypoglycaemia in alcoholics can be exacerbated by a reduced ability to secrete some of the hormones involved in the control of lipolysis (e.g. cortisol and growth hormone) and results in a decrease in the rate of fatty acid release in starvation. Alcohol-induced severe hypoglycaemia can also result in irreversible neurological changes by causing irrecoverable damage to neurons and persistent disruption of cerebral functions (15).

Ketoacidosis

Alcohol ingestion can cause ketoacidosis in people with diabetes and non-diabetics, as a result of relative insulin deficiency. Starvation, causing a depletion of glycogen stores and alcohol metabolism, leads to an increase in $NADH/NAD^+$ ratio which inhibits gluconeogenesis. This is responsible for causing an increased glucagon/insulin ratio, which increases ketogenesis (16,17). Diabetic ketoacidosis is a potentially life-threatening condition and requires prompt diagnosis and treatment of dehydration and metabolic abnormalities. Alcohol-induced ketoacidosis can be further complicated by hypoglycaemia (however it more commonly presents with hyperglycaemia).

LACTIC ACIDOSIS

The metabolism of alcohol increases the ratio of NADH to NAD^+ which inhibits the entry of the precursors of gluconeogenesis, i.e. glycerol, lactate,

alanine and other amino acids into the hepatocyte (13). The accumulation of lactate increases the risk of lactic acidosis, which is especially serious and potentially life-threatening for those people with diabetes who are treated with a biguanide.

ENDOCRINE DISTURBANCES

Chronic alcoholism can also affect gonadal function and lead to testicular atrophy, gynaecomastia (enlargement of male breasts) and sterility. It is not known what the exact mechanism for these changes is, but it is thought to be a result of reduced liver function. This reduced liver function decreases the rate of metabolism of female sex hormones, thereby leading to an increased level of circulating oestrogens. A second mechanism is thought to be that alcohol reduces synthesis of testosterone (18). Testosterone synthesis involves many steps and some of the intermediates may be dependent on the $NAD^+/NADH$ concentration ratio which, as has already been discussed, is affected by alcohol consumption.

HYPERTENSION

The UK Prospective Diabetes Study underlined the importance of well-controlled hypertension for people with Type 2 diabetes to reduce the risk of microvascular complications. There is a direct/empiric relationship between alcohol intake and blood pressure. Some researchers have found this relationship to be J-shaped (19), others U-shaped, but there is agreement that light to moderate drinkers have lower blood pressure than those who abstain and blood pressure rises steeply with heavier intakes. In heavy drinkers ingesting >300 g or 30 units per week there is a four times greater risk of stroke than in non-drinkers (20), whereas moderate alcohol consumption, up to two drinks per day, is protective for ischaemic stroke (21). Alcohol consumption showed a clear positive correlation with the subsequent development of haemorrhagic stroke but did not show a correlation with the thromboembolic variety (22). Although blood pressure is important in thrombotic stroke, alcohol's metabolic effects may exert a counterbalancing protective influence against the occlusive atherosclerotic process, as might be the case for coronary heart disease (19). So although moderate alcohol intake is cardioprotective, greater alcohol intake can neutralise the effect by having an adverse effect on blood pressure (23). The INTERSALT and British Heart Study found that the effect on blood pressure from alcohol is similar to that of obesity and greater than that for salt in the populations studied.

A reduction in systolic blood pressure of 5 mmHg achieved by favourable lifestyle changes would reduce coronary mortality by 9%. Epidemiological evidence suggests that light to moderate drinkers who stop drinking may increase

their coronary mortality by up to 10% compared to heavier drinkers who stop drinking, who may experience a 4 mmHg fall in systolic pressure and possibly a 27% reduction in coronary mortality [Klatsky, 1992, cited in Bulpitt (24)].

Studies show a link between increasing alcohol intakes and higher blood pressure. Klatsky (19) cites the Framingham Study as showing that the prevalence of hypertension ($\geqslant$160 mmHg systolic or $\geqslant$95 mmHg diastolic) was about two times higher among persons drinking 60 ounces or more of alcohol per month (57 g/day) than among those drinking less than 30 ounces per month (28.5 g/day). Also the Los Angeles Heart Study showed a significant increase in blood pressure for men who drank alcohol three or more times weekly compared to those who drank less than three times weekly or who were non-drinkers. Blood pressure is acutely affected and hypertension is resolved in those who stop drinking (6).

The 'Kaiser Permanente' investigation looked at the effect of ethnicity and found African–American men reached a maximum blood pressure at a lower alcohol intake. Among women of all races, blood pressure was lower in light to moderate drinkers than non-drinkers (25,26). All these studies were carried out in the general population not in people with diabetes, however considering the link between diabetes and hypertension and the importance of tight blood pressure control in reducing the risk of complications, recommendations regarding alcohol intakes should be cautious.

CORONARY HEART DISEASE

Light to moderate alcohol consumption is associated with a similar reduction in CHD risk among diabetic and non-diabetic men and women (27,28). Among the mechanisms accounting for the risk reduction are increased circulating concentrations of HDL cholesterol, inhibition of blood coagulation and the presence of antioxidant substances which reduce oxidative damage (Table 13.2). However, it is also well established that alcohol increases plasma triglyceride. Alcoholic hyperlipaemia results primarily from increased hepatic secretion of VLDL and secondarily from impairment in the removal of triglyceride-rich lipoproteins from the plasma. Raised triglycerides are also a feature of the

Table 13.2 Potential benefits of moderate alcohol intake

Increase in total HDL cholesterol
Increased fibrinolytic activity
Decreased platelet aggregation
Reduced incidence of myocardial infarction
Reduced insulin resistance – lower risk of developing Type 2 DM

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Table 13.3 Risks of heavy alcohol intake

Short term	Long term
Decreased gluconeogenesis	Increased risk of neuropathy
Hypoglycaemia	Increased risk of obesity and malnutrition
Increased insulin resistance	Increased frequency of accidents, gastritis, psychiatric problems
Hyperglycaemia	Liver disease
Increased free fatty acids, ketones, ketoacidosis and lactic acidosis (if treated with metformin)	Increased risk of breast and other cancers
Increased triglycerides	Pancreatitis
Hypertension	Cardiomyopathy/heart failure
Pancreatitis	

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metabolic profile of Type 2 diabetes, together with small dense LDL and low concentrations of HDL cholesterol. Hypertriglyceridaemia is an independent risk factor for coronary artery disease especially for people with Type 2 diabetes; reduction of alcohol intakes; tight glycaemic control and weight loss can help to reduce this risk (29). In subjects with alcohol-induced hypertriglyceridaemia, alcohol withdrawal has beneficial effects on the LDL profile by shifting the particle size from small to large, thus reducing susceptibility to oxidation.

With moderate alcohol consumption the increase in HDL becomes the predominant feature in the reduction of CHD risk and maximal benefit appears to be at the level of one drink per day (30). In irregular binge drinkers the increase in HDL cholesterol is not seen, adverse changes in LDL are acquired (31) and cardiovascular risk increases (Table 13.3).

Antioxidants in alcoholic beverages, especially polyphenolic compounds in red wine, have been proposed as an important contributory factor to the protective effect of regular alcohol use against atherosclerotic cardiovascular disease, by reducing oxidative damage to LDL, reducing its potential atherogenicity. The unique cardioprotective properties of red wine reside in the action of flavonoids which are minimal in white wine (except champagne). These flavonoids, especially resveratrol and quercetin, confer more potent antioxidant properties than alpha-tocopherol (32). These phenolic compounds found in wine are also thought to decrease platelet aggregation and prevent thrombus formation.

INSULIN SENSITIVITY

Moderate alcohol consumption among healthy subjects may be associated with increased insulin sensitivity and a reduced risk of diabetes (28). Reaven and

co-workers (33) found that light to moderate alcohol consumption is associated with enhanced insulin-mediated glucose uptake, lower plasma glucose and insulin concentrations in response to oral glucose in healthy men and women. For people with diabetes, light to moderate alcohol intakes with meals do not substantially alter the blood glucose concentration (34,35). However, heavy intakes may be associated with an increase in glucose intolerance. So the effect on insulin sensitivity depends on the amount of alcohol consumed (36).

OBESITY

Whether or not the consumption of alcohol constitutes a risk for weight gain and 'whether alcohol calories count' has been widely debated. Alcohol is utilised as an energy substrate by the body, contributing 7 kcal/g to energy intakes, however, unlike other energy sources, there is no immediate storage mechanism in the body. The net efficiency of energy utilisation is lower from alcohol than for fat and carbohydrate and its thermogenic effect has been assessed as 15% from acute doses (38). Lieber (39), when proposing the microsomal ethanol oxidising system (MEOS) for metabolising alcohol, hypothesised that in heavy drinkers this is uncoupled and energy from alcohol is dissipated.

Another major issue for body-weight regulation is the extent to which alcohol spares other energy substrates from oxidation (40). As alcohol cannot be stored readily it is oxidised at a steady rate in preference to other substrates, thus being carbohydrate- and fat-sparing.

There is no evidence that consuming alcohol under isoenergetic conditions, i.e. replacing carbohydrate or fat calories with alcohol calories, increases the risk of obesity. Indeed some researchers have found an inverse relationship between alcohol intake and BMI and adiposity, despite an increase in total energy intake (41). Further research is needed to investigate the extent to which alcohol calories taken in addition to 'normal' diet increase the risk of weight gain.

NEUROLOGICAL EFFECTS

The acute neurological effects of alcohol include a lowering or removal of inhibition, stimulation, an antidepressant effect and increased aggressiveness. Longer-term effects include brain damage, physical dependence (on alcohol) and sleep disturbances. It is thought that these effects are mediated through the involvement of biogenic amines (dopamine, noradrenaline, 5-hydroxy-tryptamine).

NEUROPATHY

Neuropathy is any disease of the peripheral nerves, usually causing weakness and numbness. Neuropathy is a complication of both diabetes and excessive

alcohol intakes. Therefore the risk of neuropathy increases when diabetics regularly drink more than the recommended levels of alcohol (42), and there is a direct and linear relationship between increasing alcohol intakes and worsening symptoms of neuropathy.

IMPOTENCE

There is some evidence of a correlation between heavy alcohol intakes and an increased risk of impotence in men with diabetes compared to those who report moderate intakes (43). In people with diabetes and non-diabetics there is an increased risk of functional loss of peripheral sensory and motor nerves and autonomic neuropathy with chronic heavy alcohol intakes.

SUMMARY

Evidence from many studies in the general population points to beneficial effects of small to moderate daily intakes of alcoholic drinks, but there is also strong evidence of the risks of heavier intakes. For the person with diabetes perhaps the most concerning of these risks is the impact on blood pressure, particularly for African–Caribbean men (at lower intakes), dramatically increasing the risk of stroke.

For people with Type 2 diabetes small to moderate daily intakes can improve their metabolic profile and reduce CHD risk by raising HDL cholesterol, increasing insulin sensitivity, increasing fibrinolytic activity, reducing platelet aggregation, improving antioxidant status and improving blood pressure.

For people with Type 1 diabetes the benefits of small to moderate intakes are similar to those for the general population, but the risks from heavier intakes are severe hypoglycaemia (which can be mistaken for intoxication) or ketoacidosis.

There is a need for further work to accurately evaluate at what level of alcohol intake the risks outweigh the benefits, as most of the studies use self-reported data, which because of underestimation could mean there is a lower apparent threshold of alcohol-related effects.

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